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THE EFFECT OF LIVER EXTRACT ON THE SMALL INTESTINE OF PATIENTS WITH SPRUE.

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A clinical study of a relatively large group of patients with sprue has been made over periods of from 1 to 3 years following remissions of the disease induced by liver extract therapy. During this study it has been observed that flatulence, intestinal discomfort, cramps and diarrhea recurred unless a sufficiently large amount of liver extract was administered at frequent intervals. This was the case despite the fact that no detectable hematological disturbance was present. Thus the intestinal dysfunction rather than the anemia has been the guide for the administration of therapy. The fact that the amount of liver extract necessary to prevent recurrence of intestinal dysfunction was far greater than that necessary to maintain normal blood levels, suggested that a relationship existed between liver extract and intestinal activity. The results of the roentgenologic study of an individual case which are presented in this communication bear out this suggestion.

Characteristic morphologic alterations of the small intestine of patients with sprue have been demonstrated roentgenologically by Mackie, Miller and Rhoads.[1] The extent of the abnormalities were shown to vary directly with the severity of the clinical picture and furthermore a return to a state more nearly normal was demonstrable after adequate therapy had been administered. These

abnormalities may be summarized as follows: 1, a segmental distribution of barium, produced, it is inferred, by abnormal motility of portions of the small intestine; 2, a variation in contour and caliber of the intestinal segments; 3, a distorted mucosal pattern, especially of the duodenum and jejunum, but often of the ileum as well; 4, an outline of the terminal ileum which appears straighter than normal and gives the impression of a lack of pliability of the intestinal wall.

In the course of this study an opportunity was presented for the investigation of a patient who had diarrhea regularly if liver extract was withheld for periods of from 10 days to 2 weeks. In this instance the changes in the small intestine were visualized by Roentgen ray both during an attack of diarrhea and immediately following the cessation of symptoms which followed liver extract therapy. The results are striking in that they furnish unequivocal evidence of the specificity of liver extract therapy of the intestinal manifestations of sprue without anemia.

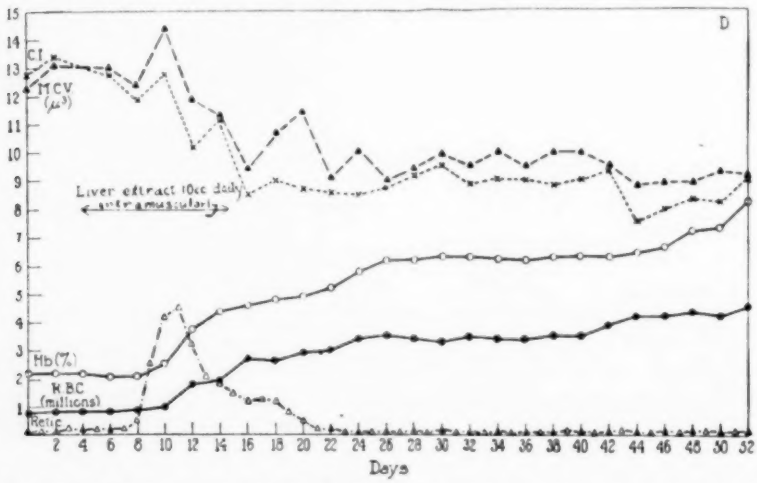

CHART I.—Hematological changes following the daily administration of 10 cc. liver extract intramuscularly.

Clinical History (Chart I). An American woman, aged 50, who had lived for 21 years in southern China, entered the hospital complaining of diarrhea of 7 years' duration. Her illness began with an acute, afebrile attack of diarrhea lasting 6 weeks. Subsequent attacks occurred during the first year. Early in the second year, soreness of the mouth and the tongue developed, and the diarrhea was persistent. Relief of symptoms followed the use of a diet of sour milk and liver. During the fourth year of the illness improvement did not follow the same treatment and the patient returned to this country, where she was symptom-free for 6 months. This period of relief was again followed by severe abdominal distress and diarrhea. About 6 weeks before entry, weakness, shortness of breath and pallor appeared, and she was confined to bed. Three vials of liver extract, Lilly, were administered orally each day without improvement.

FIG. 1.—Roentgen ray of small intestine 2¼ hours after barium meal during an attack of diarrhea showing two columns of barium and residue in stomach.

FIG. 2.—Roentgen ray of small intestine 3¼ hours after barium meal, during an attack of diarrhea, and showing segmental arrangement of barium in the ileum.

Fig. 3.—Roentgen ray of small intestine 2 hours after barium meal, 4 days after preceding Roentgen ray study and after diarrhea had ceased (compare with Fig. 1).

Fig. 4.—Roentgen ray of small intestine 3¼ hours after barium meal and after diarrhea had ceased (compare with Fig. 2).

Examination. The patient was markedly emaciated and appeared extremely ill. The skin and mucous membranes had a lemon-yellow tint and were pale. There was atrophy of the papillæ along the borders of the tongue, with furrows over the dorsum. The abdomen was slightly distended and tympanitic. The spleen was palpable. There was pitting edema of both ankles. Gastric analysis showed free hydrochloric acid only after the injection of histamin. Laboratory examination showed: red blood cells, 820,000; hemoglobin, 22%; color index, 1.34; mean corpuscular volume, 131 cubic microns; icteric index, 20; reticulocytes, 1%.

Course in Hospital. Daily intramuscular injections of liver extract (Eli Lilly & Co.) were given for 2 weeks. Each injection was of 10 cc., an amount derived from 50 gm. of whole liver. On the 6th day after the first injection there was a rise in the number of reticulocytes to 42%. The day after the first injection the patient had one formed bowel movement, although there previously had been 5 or 6 loose stools daily. The rise in the number of reticulocytes was followed by an increase in the number of erythrocytes and the hemoglobin. The patient had no further diarrhea unless a longer period than 2 weeks elapsed between injections of liver extract. She was discharged 7 weeks after entry with an erythrocyte count of 4,170,000 and a hemoglobin of 73%.

The patient has been followed for the past 3 years. During this time the erythrocyte count and the hemoglobin have been maintained at normal levels. There have been no diarrhea or intestinal symptoms except when a period longer than 10 days to 3 weeks elapsed between the injections of liver extract. The patient can determine the necessity for treatment by the appearance of flatulence, cramps and finally diarrhea. At no time has liver extract failed to relieve all intestinal symptoms within 24 hours.

The patient was readmitted to the hospital during an attack of diarrhea induced by withholding liver extract therapy. During this admission roentgenologic study of the small intestine was made and was compared to one done 4 days later, subsequent to the injection of liver extract and the relief of intestinal symptoms.

The method of Roentgen ray examination of the small intestine used in this study was that described by Mackie, Miller and Rhoads.[1] Two ounces of barium were given to the patient 1 hour after a light breakfast. Roentgen ray pictures were taken 15 minutes later and at 30-minute intervals the head of the barium column had reached the cecum. Reëxaminations were then made at hourly intervals until the small intestine was empty. The barium was given after a meal so that the motility of the small intestine would be as normal as possible.

The Small Intestine During an Attack of Diarrhea (Figs. 1 and 2). At $\frac{1}{4}$ hour the second portion of the duodenum was dilated and the rugæ were wider than normal. At $1\frac{1}{4}$ hours the upper jejunum showed a definitely abnormal mucosal pattern and was widened. A segmental progression of the barium was indicated by two distinct segments of small intestine which contained the radio-opaque substance. At $2\frac{1}{4}$ hours an even more marked segmental distribution was in evidence, as well as a variation in caliber and an irregularity of the contours of the isolated intestinal segments. At $2\frac{3}{4}$ hours the upper jejunum was empty and a segmental distribution of barium throughout the whole small intestine distal to the upper jejunum was found. Marked variation in caliber of these isolated segments was apparent, some being constricted and others markedly dilated. These changes are frequently seen in sprue and are almost invariably found when diarrhea is present. The barium reached the cecum in 5 hours, while at $6\frac{3}{4}$ hours a definite gastric residue was seen in the stomach, and the terminal ileal segments still contained barium.

The Small Intestine Subsequent to the Administration of Liver Extract Followed by Cessation of Diarrhea (Figs. 3 and 4). At $\frac{1}{4}$ hour and 1 hour

the same changes in the duodenum and jejunum were seen as in the previous study. At 1 hour, however, the stomach was nearly empty and the barium appeared to be travelling through the small intestine in a continuous column. Marked variations in the caliber and outline of the intestine were present. At 2 hours the stomach was empty. The head of the barium column had reached the cecum at $2\frac{3}{4}$ hours. No segmental distribution of barium was seen. At 5 hours the small intestine was empty.

The segmental distribution of the barium throughout the small intestine which was such a striking feature in the previous study had disappeared. The barium presented a continuous smooth outline throughout the small intestine. These changes are interpreted as indicating a restoration toward normal of the motor function of the small intestine.

Discussion. The study presented demonstrates an effect of liver extract on the functional activity of the small intestine in patients with sprue. The arrangement of the radio-opaque substance in isolated intestinal segments which was seen when diarrhea was present was not a feature 4 days later, after liver extract had been administered and diarrhea had ceased. Similar results have been seen in other patients of this series, but in none was the picture as dramatic as in this instance. These results demonstrate the therapeutic specificity of liver extract in sprue without anemia.

Clinical observation has shown that patients with sprue[2] or pellagra[3] require much larger amounts of liver extract than do patients with pernicious anemia. This applies even to liver extract therapy administered parenterally, a route which excludes the possibility of a lack of absorption or of destruction of the material in the gastro-intestinal tract. This fact, together with the observation that in patients with sprue a much larger amount of liver extract is necessary to prevent diarrhea than is required to maintain normal blood levels, suggests that either different fractions of liver extract are operative in sprue and pellagra from those which are effective in pernicious anemia, or that the therapeutic actions of the same substance varies in the three disease states. The conditioning of the functional activity of the small intestine may possibly be another therapeutic function of the antipernicious anemia substance. The answer to this problem awaits further investigation.

Summary. 1. Roentgenologic evidence of abnormal form and function of the small intestine of a patient with sprue, without anemia but with diarrhea is presented.

2. A return toward normal form and function, as evidenced by roentgenologic study, as well as the disappearance of symptoms followed the injection of liver extract.

3. It is suggested that liver extract administered parenterally conditions the functional activity of the small intestine.

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ACUTE BASOPHILIC LEUKEMIA.

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It seems to be true that rare cell-type leukemias and leukemic states do occasionally occur. Subscribing as we do to the principle that in any given leukemia there is an abnormal, immature, imperfect leukoblastic type cell proliferating and invading without normal maturation,[11,12] in time and full experience, one would expect to find leukemia cells resembling every normal type. Resemblance only, partial, imperfect differentiation only, varying degrees of resemblance to be sure, not always even a recognizable resemblance, for leukemia cells are sometimes exceedingly primitive and bizarre.

Hay and Evans[1] review the few reported cases of eosinophilic leukemia adding an acute case of their own, all previous authenticated cases having been chronic ones. There has been added recently the case of McCowen and Parker,[2] an acute eosinophilic leukemic state with leukemic infiltrations showing eosinophils.

Joachim,[3] in 1906, reported 2 cases of chronic leukemia in both of which the percentage of "mast cells" was above 50%. The first was followed for 5 weeks, discharged, and lost track of; the second for but a 17-day period, but giving a history of a diagnosis of leukemia made elsewhere 7 months previously at which first examination some 500,000 leukocytes were found. The blood picture was that of an ordinary chronic myeloid leukemia except for the large number of "mast cells," as high as 83%.

Joachim's opinion was that the general symptoms being similar to other chronic myeloid leukemias except for the degree of basophilic increase, one should be loath to call it a separate type of leukemia. He reported it as an atypical leukemia, concluding that chronic basophilic leukemia is a variety of the common myelocytic variety. He found the prognosis more unfavorable, and the mast cells radioresistant.

General infiltration characteristic of the chronic leukemias was found at autopsy. It was noteworthy that he had great difficulty in staining autopsy tissues. The basophil or mast cell granules disappeared. He got his best results with polychrome blue, but even then the granules were not distinctive. Such granules as were preserved showed varied stain affinity, from clear violet to bright red, like eosinophilic granules.

Sabrazès[4] was most interested in proving the differentiation of hemohistioblasts to mature mast cells. The so-called hemohistioblast of Ferrata and many types of basophils he had frequently found increased in chronic myeloid leukemia. He concluded that his case was one of chronic myeloid leukemia with an abundance of "granular basocytes." He believed such cases are relatively common and particularly resistant to both Roentgen ray and benzol. Using May-Giemsa stain, he noted variations in size of cell, size and distribution of granules, and a varying character of nucleus convincing him that he had supporting evidence in agreement with his previous views.[6] He maintained that mesenchymal hemohistioblastic cells have the capability of differentiating directly into the common granular basophilic cells. The blood in his case returned almost to normal after Roentgen ray treatment, except for the persistence of mast cells and the so-called hemohistioblasts. Four months after the first examination,[5] mouth lesions, cough, fever and a leukemic blood picture appeared. There were even more mast cells and hemohistioblasts than before, definite left shift in the leukocytes generally, and a severe anemia. No marrow biopsy is reported. The platelets were uneven and few in number and many of these few were large and globular. Among the white cells mitotic figures were said to have been found, the type of cell unfortunately not stated. Eventually the myeloblast became the dominant cell, 32% of the total number, the mast cells 20%.

Sabrazès[6] discussed the morphologic characteristics of basophilia under pathologic conditions. His observations and those of Di Guglielmo[7] may lead us away from our present not too clear conceptions of the origin of basophils, mast cells and, incidentally, monocytes.

Sarzi-Sartori's[8] case is practically a counterpart of Sabrazès'. He agrees with Joachim that one should be cautious about calling these cases mast-cell leukemia. His case showed 45% basophils and many hemohistioblasts. Although he had never seen the cell described by Di Guglielmo[5] on which Sabrazès sets great store, he accepts their theories.

Elliott and Young[9] reported a case called chronic mast-cell leukemia because of predominance of leukocytes with coarse basophilic granulation. They speak of the frequency of association of increase of both eosinophils and basophils in chronic myeloid leukemia and would restrict the term "mast-cell leukemia" to those

cases in which the basophilic leukocytes are the principal feature of the blood smear. The basophils reached 64% and were very coarsely granulated and mature. Roentgen ray treatment and benzol decreased the total leukocytes principally by reducing the adult neutrophils. The basophils steadily increased. Autopsy was referred to as revealing a splenic infarction but no other details were given.

Our case may be summarized as follows:

Case Report. A man, aged 27, dentist, was referred by Dr. Frank Stradling, Earlville, N. Y., September 13, 1935. He stated that March, 1935, he tired easily and lost weight. Appetite was poor and he slept fitfully. There was gastric distress, belching, and abdominal distention and a hard mass in the left upper abdominal quadrant. He noticed spongy gums with some bleeding and there was nosebleed. Having had laboratory training, he thought of the possibility of leukemia, examined his own blood and made his own diagnosis. He was seen by Dr. Roy G. Pfotzer, of Buffalo, N. Y., March 29, 1935, who noted: "He complained of malaise, anorexia, loss of weight, loss of color and a lump in the left side. Pale, well developed, fairly well nourished, the spleen was at the level of the umbilicus; temperature, 100.2° F. A blood count showed: Hb. (Dare), 64%; R.B.C., 3,800,000; W.B.C., 186,000; polys, 60%; myelocytes (principally neutrophilic), 35%; lymphocytes, 5%. A rare blast form was noted. At this time no basophilic element was present.

	W.B.C.	Myelocytes, per cent.
April 2	85,000	18
10	80,000	17
22	12,600	4
May 6	6,400	1
20	6,800	1
June 1	5,600	1
17	9,400	5
30	14,200	6

"His weight at first examination was 185; on June 30, when last seen, it had risen to 210, and at this time his R.B.C. was 4,540,000; Hb., 94%. The spleen receded and was not palpable on April 22. At no time during the blood studies was there a basophilic tendency."

He had 9 light Roentgen ray treatments to the splenic area (Dr. J. M. Barnes, of Buffalo), and large doses of iron by mouth. He was told that his blood was practically normal, but warned of recurrence and instructed to continue under observation. July 19, 1935, at the Norwich, N. Y., Hospital, his blood showed: W.B.C., 10,200; small lymphocytes, 16%; large mononuclears, 3%; neutrophils, 78%; eosinophils, 1%; basophils, 2%. Again there, August 21: W.B.C., 9500; lymphocytes, 20%; mononuclears, 4%; neutrophils, 74%; basophils, 2%.

About September 1 he began having gastro-intestinal disturbances, restlessness and all the other symptoms previously described, including the firm abdominal mass. Dr. Johns, Utica Memorial Hospital, reports, September 7: W.B.C., 39,500; polys, 67%; filament cells, 8%; non-filament cells, 59%; lymphocytes, 18%; transitionals, 3%; basophils, 12%; abnormal erythrocytes, none; abnormal leukocytes, myelocytes, also myeloblasts, 50 cells in 100.

On the strength of this blood finding he had a Roentgen ray treatment of 185 R's broadly over the left abdomen, given by Dr. Lee Hadley.

Dr. Stradling felt that the symptoms had suggested a possible peptic ulcer or malignancy in addition to the leukemia.

Physical Examination (Dr. Groat).—A remarkably well-built, clear-skinned, alert young man, 6 feet 3 inches tall, still weighing just over 200 pounds. Restless and apprehensive, but truly remarkably well in hand considering the fact that he knew all about his condition. The gums were soft, spongy and there were small clots in the margins next to the teeth; there were some small areas of ecchymosis on the buccal mucous membrane and a small clot behind the anterior pillar of the right tonsil. There was a multiform erythematous rash with itching, quite like an allergic rash, possibly due to the considerable amount of phenobarbital taken the previous 2 weeks. The neck, chest, lungs, mediastinum and heart appeared normal. A mass, evidently an enlarged spleen, reached 12 cm. below the left costal border and well toward the midline. There were some good-sized ecchymotic areas on the back; there was definite epigastric tenderness with tympanites and distention. The liver lower margin could just be felt. There were no palpably enlarged lymph nodes. The urine and blood aside from the abnormalities shown in the tables were not remarkable.

Progress. Continuous fever, increasingly bothersome nasal hemorrhages and oozing, bloody vomitus and new areas of ecchymosis. Frequent epigastric distress relieved somewhat by CO^2 and oxygen and he expired in coma at 5 P.M., October 5. Temperature ranged from 99.6° to 101° F. the first week, reached 103.6° F. following a transfusion in the second week, more irregularly, 100° to 103° F., during the third week and continuously 101° to 102° F. the final week, the pulse gradually working upward from the 80's to a running pulse of 120 to 140 in the final week.

Treatment. Since both general condition and blood state became definitely worse following the Roentgen ray treatment, acute leukemias being seldom benefited thereby, no further treatments were given. Twice a citrate transfusion of 300 cc. of blood was given and after each the patient was decidedly uncomfortable, once alarmingly depressed and at no time appreciably benefited despite the fact that the blood was carefully matched. The reactions were 24 to 48 hours afterward in both instances, the temperature rising to 104° F. without chill. He desired not to have any more transfusions and it seemed humane not to insist upon them in any revised form.

The only medication, other than sedatives, was liver extract intramuscularly, which in our experience has been somewhat helpful in other cases of acute and chronic leukemia, more particularly in the latter. But these injections were discontinued during the last week because they became so objectionable to the patient. He asked to have iron, so a preparation of citrate of iron was given him by mouth the last few days. This placebo of iron seems to account for the black, granular, semisolid stools which he had on the last day.

Necropsy (Dr. Wyatt, 2½ hours after death). On external examination the only significant findings were marked pallor of skin and mucous membrane and a small healing puncture wound over the middle of the head of the sternum made for marrow biopsy. The serous cavities showed no significant lesion. There was rather marked pallor of the myocardium, liver and kidneys, without other gross lesion. The lungs showed numerous small scattered hemorrhages but no gross evidence of inflammatory or leukemic infiltration. The spleen was rather markedly enlarged, weighing 1045 gm. On section its cut surface was fairly firm but somewhat friable, and the normal splenic markings were not evident. In the duodenum just beyond the pyloric ring there were two separate, typically punched-out, peptic ulcers, each of which measured approximately 1 cm. in diameter. One of the ulcers was on the superior wall and was firmly

adherent to the neck of the gall bladder, while the other was on the posterior wall and was adherent to the pancreas. There were no large bloodvessels exposed in the ulcers. The contents of the intestines were somewhat blackish, but not definitely tarry in consistency. (Iron citrate had been administered.)

The bone marrow as observed in the ribs and head of the sternum was not remarkable in its gross appearance. The marrow cavity of the middle third of the right femur was filled with abundant, rather firm, mottled reddish and grayish marrow which was definitely adherent to the walls of the cavity. The inner surface of the compact bone forming the wall of the marrow cavity was distinctly roughened, due to the presence of a layer of marrow, 1 to 2 mm. thick, which was mixed with loose, spongy bone. Direct smears of the marrow from the femur, ribs and sternum were made, in addition to the taking of blocks of tissue for sections, which were prepared with the usual paraffin technique and stained with hematoxylin and eosin.

Microscopic Findings. There was slight degeneration of the myocardium, but not to the degree which was suspected from the gross pallor and mottling. The sections of the lungs showed hemorrhage, slight edema, and small areas of bronchopneumonia. There was no evidence of leukemic infiltration in the sections of myocardium, lungs, or kidneys. The walls and floors of the duodenal ulcers showed only inflammatory reaction and necrosis, without definite invasion by leukemic cells.

Spleen. There was complete loss of normal splenic architecture and replacement by a picture very similar to that seen in the bone marrow. This was made up of more or less evenly distributed leukoblasts of various types, erythroblasts, a few megakaryocytes, intermingled with mature leukocytes and stroma cells. In places there was more or less fibrosis. The cells which stood out most clearly and were most easily classified as myelocytes were eosinophilic. These were quite numerous. In addition, there were numerous other cells of about the same size and with nuclei of about the same character, but without definite granules in the cytoplasm; these were presumably either neutrophilic myelocytes or basophilic myelocytes which had undergone such changes in the cytoplasmic granules as to render them undemonstrable in those sections. The presence of such basophilic cells in large numbers in the direct smears of marrow and their absence in the sections of marrow and spleen, even when stained with the same blood stain as the smears, would suggest that the granules are easily lost in the preparation of sections. This has also been the experience of others in studying similar cases.[3] In addition to these myelocytic cells there were numerous larger cells with a small amount of non-granular cytoplasm which probably were myeloblasts. In certain instances these seemed to be definitely grouped to form areas which stood out from the surrounding cells. Erythroblasts were relatively inconspicuous, as were also the megakaryocytes.

Liver. In the connective tissue of the portal canals there was considerable myeloid tissue similar to that described in the spleen. There was also definite necrosis of liver cells in varying degrees in the centers of the lobules.

Bone Marrow. The marrow was very cellular, the leukoblastic elements markedly predominating over the erythroblastic, giving the impression that the latter were crowded out. The structure was somewhat similar to that described in the spleen, except that it was more cellular. Eosinophilic myelocytes were present in large numbers; also there were very numerous myelocytes which were probably divided between the basophilic variety shown in the direct smears and the neutrophilic type. There were also very numerous large atypical cells, probably of primitive myeloid type. Megakaryocytes were found rather infrequently, and for the most part

tended to be young, active forms. The grouping of myeloblasts or myelocytes of a certain type was rather striking in places, large fields being made up almost entirely of similar cells. Mitotic figures were found rather frequently in certain areas of the sections whereas in other portions they were found infrequently. It was difficult in all instances to be sure of the type of cell in mitotic division; but some of them were large and nongranular while others were smaller and probably myelocytes of either the neutrophilic or basophilic type and very few erythroblasts. No mitotic figures were found in eosinophilic myelocytes.

Summary of Macroscopic and Microscopic Findings. Some degeneration of myocardium. Bronchopneumonia. Two duodenal ulcers. Splenomegaly with myeloid leukemic infiltration. Some leukemic infiltration in portal canals of liver. Central necrosis of liver. Myeloid hyperplasia of bone marrow, largely replacing erythroblastic tissue and megakaryocytes.

TABLE 1.—(MISS F.)

Date, 1935.	Hemoglobin.	R.B.C.	W.B.C.	Neutrophils.	Lymphocytes.	Mononuclears.	Promyelocytes. Myelocytes. Metamyelocytes. / Neutrophilic.	Eosinophilic. / Granulocytes.	Basophilic. / Granulocytes.	Eosinophilic-Basophilic. / Granulocytes.	Myeloblasts.	Others.
Sept. 13	14.0	3.3	40.1	62.0	2.5	2.0	5.0	..	24.0	0.5	3.5	0.5
14	..	..	..	57.5	5.0	3.0	10.5	1.0	21.0	..	2.0	
15	..	..	..	54.0	3.5	3.0	11.5	0.5	26.5	0.5	..	0.5
16	..	..	..	50.5	2.5	3.0	10.5	1.0	32.0	..	0.5	
17	14.0	3.6	30.0	49.0	1.5	2.5	10.0	..	32.5	0.5	3.0	0.1
18	..	..	..	44.5	3.5	3.0	12.0	..	32.5	0.5	4.0	
19	..	..	..	42.5	1.0	2.5	16.5	0.5	32.5			
20	..	..	..	38.5	2.0	..	13.0	1.0	37.0	1.0	6.0	1.5
21	..	..	..	37.5	2.0	1.0	14.5	1.0	36.5	1.5	4.0	2.0
23	12.0	3.0	75.2	31.5	1.5	2.5	11.0	1.0	44.0	1.0	4.5	0.5
24	..	..	..	26.0	1.0	3.0	8.5	0.5	55.0	..	5.0	1.0
25	..	2.2	53.6	22.5	2.0	1.5	15.0	..	50.0	..	7.5	1.5
26	5.5	2.0	61.6	25.5	1.0	0.5	5.5	1.0	61.0	..	5.5	
27	..	..	..	23.5	2.5	0.5	10.0	2.0	47.5	1.0	11.0	2.0
28	5.5	1.7	86.7	24.0	..	1.5	11.0	2.0	48.0	..	11.0	2.5
29	..	..	..	15.5	0.5	1.5	11.5	1.0	58.5	0.5	11.0	
30	3.5	1.4	118.4	14.0	..	..	9.0	3.0	57.5	..	15.0	0.5
Oct. 1	..	1.3	96.0	19.5	..	..	5.0	1.5	58.0	0.5	13.0	2.5
2	..	..	..	17.5	0.5	..	10.0	3.5	51.0	..	13.0	4.5
3	..	1.2	121.6	14.0	..	..	8.0	1.0	54.0	..	19.5	3.4
4	..	..	..	13.0	..	..	6.5	4.0	58.0	..	17.0	1.5
5	..	950.0	..	19.0	..	..	7.0	3.5	41.0	1.0	25.0	3.0

The major progressive blood changes are shown in Table 1. The additional features are that the platelets were from the first sparse, apparently never over 80,000, and highly abnormal, mostly large globular, or dumbbell shaped with occasional long streamers, and very pale staining. They did not clump normally, possibly additional evidence of qualitative deficiencies.

Reviewing the progressive blood picture, it is noteworthy that the total number of cells and the total number of basophilic and myeloblastic cells increase roughly in much the same ratio (Table 2), with the anemia in reverse ratio. There is a non-progressive left shift in the neutrophils and a progressive left shift in the basophils (Table 2). An arbitrary division of the basophils was made to permit a differential count and indicate a possible shift. These type cells may be readily recognized in the photomicrographs in

Plate I. It is noteworthy that both the large cell with fine basophilic granules and the large cell with coarse basophilic granules show some variation in the size of the granules. This variation in granule size is more marked in the two smaller mature types. We do not include as basophils basophilic proeosinophils or basophilic proneutrophils, notwithstanding the fact that others have had difficulty in separating them. There were very few such cells in the smears and they were included in their own classes. This was possible because the stain which we use, a modification of Jenners' stain not dissimilar from the May-Giemsa in its actual composition and potentialities, we believe to be superior to all others as a differentiator of granules. The granules of basophilic proeosinophils with our stain are more pinkish violet and definitely less intensively stained than are true basophil granules which stain a purple black. This stain and its results have been demonstrated[10,13] and many now use it. An article describing its manufacture and use is soon to appear in the *Journal of Laboratory and Clinical Medicine*.[14]

TABLE 2.—(MISS F.)

Date, 1935.	Basophils, percentages.					Neutrophils, percentage.		Myeloblasts, total.
	Total.	Class I.	Class II.	Class III.	Class IV.	Total.	Non-filamented polys.	
Sept. 13	9,624	26	51	4	19	24,862	30.0	1,403
17	9,750	35	46	2	16	14,700	33.0	900
23	33,088	48	40	2	10	23,688	25.0	3,384
26	37,576	57	36	2	5	15,708	29.0	3,388
28	41,616	58	32	4	6	20,808	40.0	9,537
30	68,080	61	28	5	6	16,576	36.0	17,760
Oct. 1	55,680	60	35	2	3	18,720	23.0	12,480
3	65,664	67	26	4	3	17,024	29.0	23,712

Classes of basophils:

I. Large cells with fine granules over an immature nucleus.
II. Large cells with variating coarse granules over an immature nucleus.
III. Cells, slightly smaller, with variating coarse granules in the small portion of cytoplasm.
IV. Smaller cells with fairly typical granules over a more mature clover-leaf-shaped nucleus.

A sternal marrow biopsy was done, October 1, 1935. The method of choice, trephining a plug from the sternum for smear and section, was not followed because of certain objections, and also the possibility of hemorrhage; but the method used was comparable to it in that a 12-gauge needle with blunted point and trocar was thrust into the sternum, the trocar removed, the needle then advanced and rotated, then carefully withdrawn, removing a mush

of marrow from which the smears were made and stained the same as blood and selected fields appear as illustrations (Plate II).

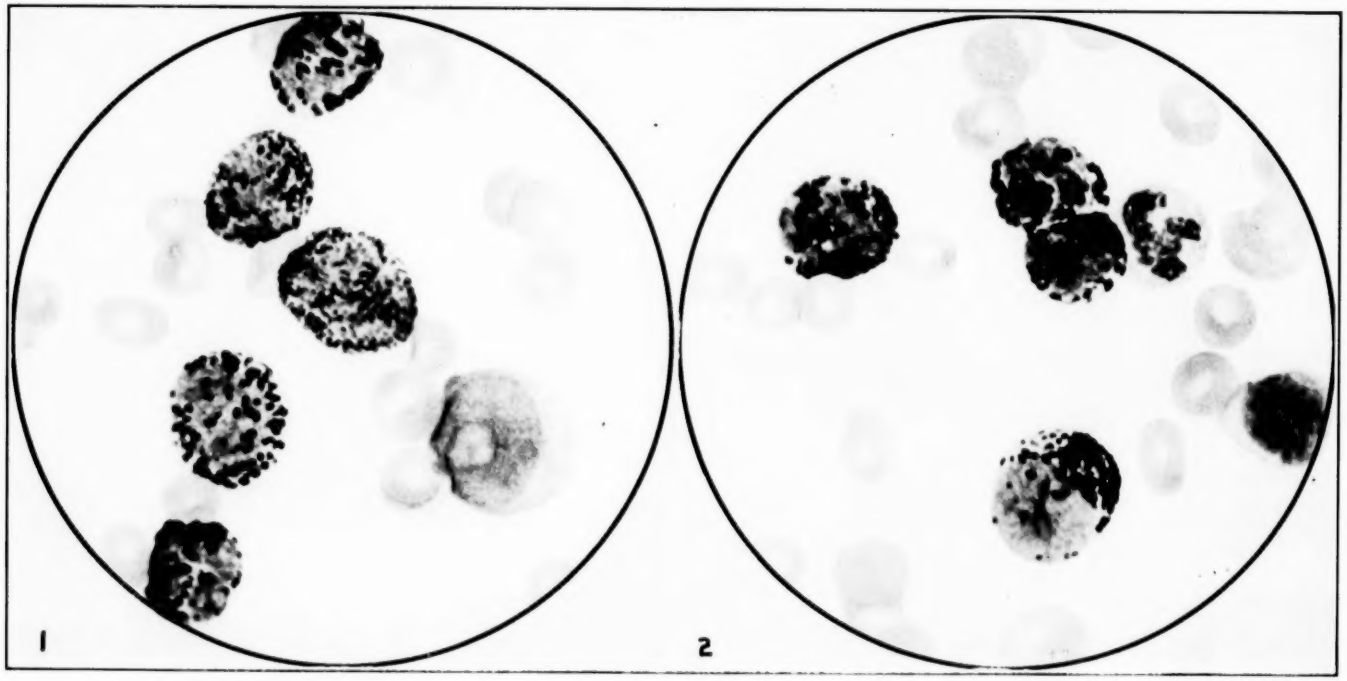
Autopsy smears of sternal marrow were stained as blood after first being extracted with ether and alcohol and typical fields appear as illustrations (Plate III).

We have been interested[12] in haploid mitotic figures in the type cell of various leukemias and have searched both blood and marrow smears of this case with diligence and found a total of 26, all in large non-granular cells such as appear in the various illustrations. A selection of these are to be found in Plate IV. So far as we could determine, many of these are haploid myeloblasts.

We find no mitotic figures in basophils. In all other cases where we have found haploid mitotic figures they have been in what would be considered the type cell of the leukemia and we have shown this.[12] We believe this to be confirmatory of the contention that a leukemic state is a type of malignant growth with immature, abnormal, imperfect cells proliferating without much differentiation.[12] Irregular mitotic division indicates cell abnormality and imperfection.

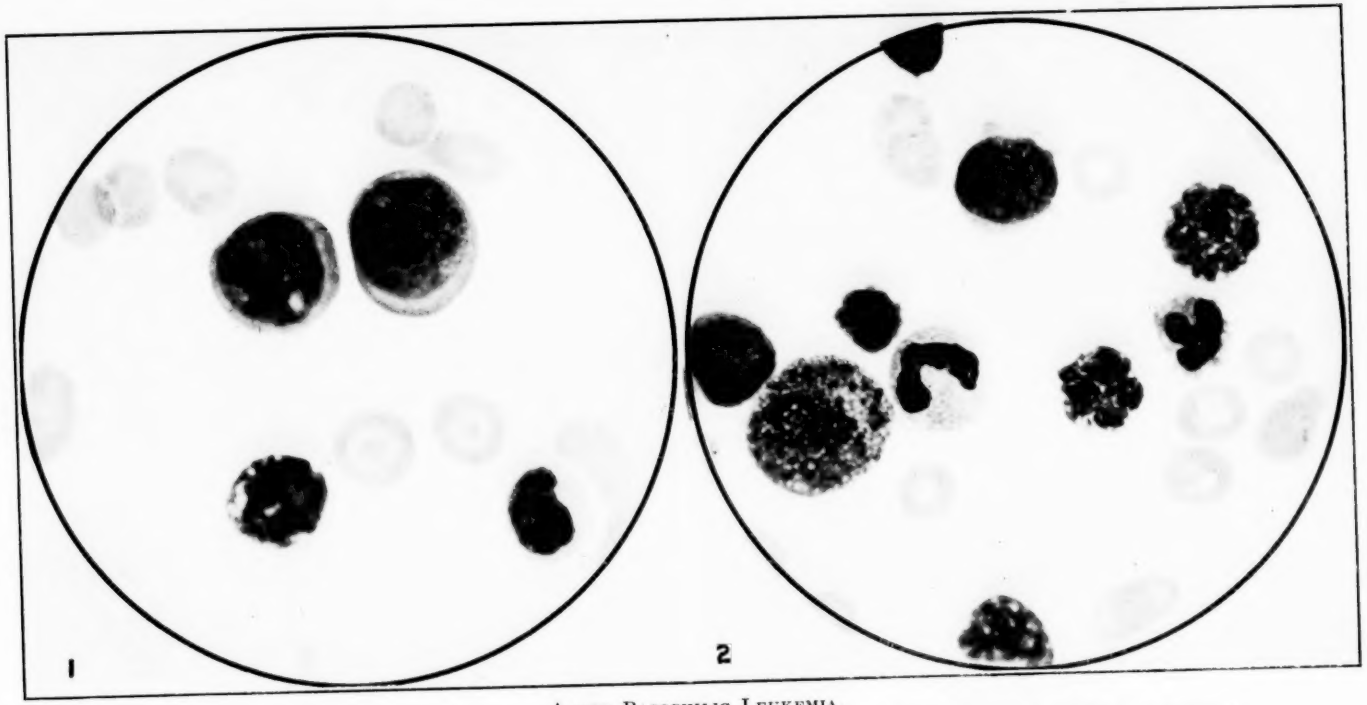
Discussion and Conclusions (Dr. Groat). We believe it important that the few reported cases of leukemia with true basophilic predominance have other common characteristics. It is also noteworthy that the few eosinophilic leukemias reported resemble each other and in certain respects resemble the basophilic cases. In the literature one finds a cautious attitude toward eosinophilic and basophilic leukemias. Practically everyone has mentioned the tendency for eosinophils and basophils to be increased in chronic myeloid leukemias. There are many cases in every hematologist's experience in which numerous basophilic and eosinophilic myelocytes and promyelocytes, and, or, plentiful mature looking mast cells and eosinophils are showy features in the stained film. They make Schilling's "gay picture." There is agreement that the basophils or eosinophils in what have been called special leukemia types keep toward the mature regardless of the company they keep. As in our case, one finds a gradual gradation of maturity so that division into classes is more or less arbitrary. We show a left shift in our case but do not confirm Sabrazès,[4] that the basophils may be traced back to the hemohistioblastic cell of Ferrata through the granular intermediate cell of Di Guglielmo.[7] We are quite familiar with these two cells, have photographed them, both in black and white and in natural color; they have been a part of our exhibits.[10,12]

The cytoplasm of these large sprawling, loosely flowing, Ferrata cells stains pale blue, the sparse granules and little rods gray violet, the large round loose-skeined nucleus pale magenta with our blood stain. The Di Guglielmo variant of this cell is smaller, more rounded, with cytoplasm more sharply defined. Either may con-



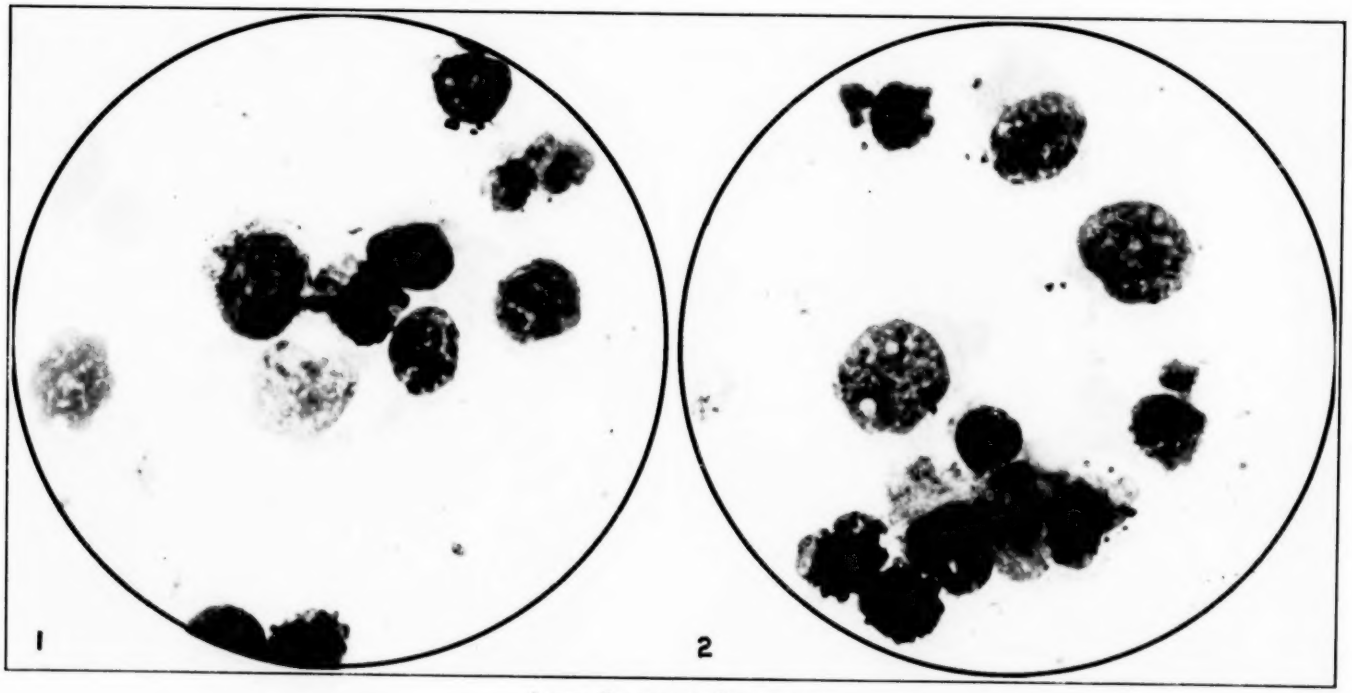
ACUTE BASOPHILIC LEUKEMIA.

PLATE I.—Photomicrographs × 1200, blood smears taken October 1, 1935, showing various types of basophilis (Miss Zimmer).



ACUTE BASOPHILIC LEUKEMIA.

PLATE II.—Photomicrographs × 1200, smears of sternal marrow obtained by biopsy October 1, 1935 (Miss Zimmer).



ACUTE BASOPHILIC LEUKEMIA.

PLATE III.—Photomicrographs × 1200, smears of sternal marrow obtained at autopsy October 5, 1935 (Miss Zimmer).

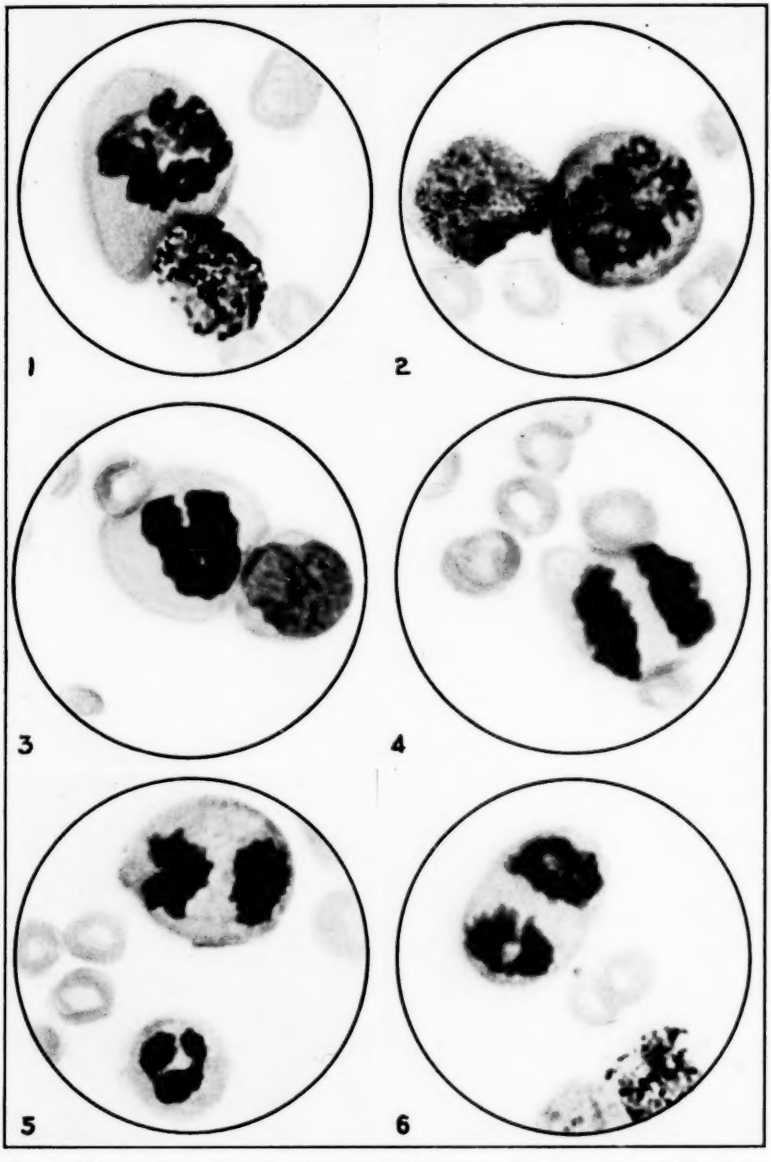


PLATE IV.—Various stages of mitotic division found in the large myeloblasts, all apparently haploids except No. 2 which may be diploid or multipolar.

tain particulate matter. We regard them as hematopoietic system cells; macrophages; clasmatocytes; possibly primitive monocytes.

Only one Ferrata cell has been found in this case notwithstanding thorough search for them. We know these cells but do not feel that Di Guglielmo[7] and Sabrazès[4] have established their point, that multipotent reticulo-endothelial cells build up azurophilic granules and rods with a nucleus of spongy reticular type with two or three nucleoli, to become the so-called hemohistioblasts of Ferrata and that these go to differentiate directly into basophilic mast cells. There is confusion caused by one thinking of the hemohistioblast solely as a blood cell while another speaks of it both as a blood and tissue cell. We are committed to the idea that blood cells found in adults are normally contained in a closed hematopoietic system which makes a special environment[11,12] to which they are suited.

Leaving the origin of the basophil and the reasons for its appearance as the predominating cell in a leukemia unexplained, the question remains, Is the basophil that is abundant in these reported cases the leukemia cell? In our case we believe it is not. We doubt whether it is in any of the cases, or that the eosinophilic cell found in the so-called eosinophilic leukemias is the leukemia cell. We do admit the possibility. There is much that indicates that others have been equally skeptical. We believe that in our study we have developed some evidence to show that the basophil is not the leukemia cell. In our case and possibly in other cases if they might be fully reviewed, if one could but remove the basophils from the picture, all the essential features of an acute myeloid leukemia would remain. We are aware of the limitations in the term "acute" in relation to leukemia. While acute myeloid leukemias are usually myeloblastic, they need not be. While acute leukemias usually run a short course, it has been customary to determine the beginning as the time when a definite illness and leukemia blood picture appear. We have been able to show, particularly in a series of leukemias in children which two of us (Wyatt and Groat) will soon report, that even this most acute type of leukemia may go for considerable time without obvious blood expression. The fact that Sabrazès' chronic case had an early less malignant phase followed by remission is not remarkable in a leukemia. We have subscribed to the idea that a preleukemic period probably always occurs,[12] and that a preliminary episode followed by a remission is by no means uncommon. In our study of leukemias in children soon to appear, one infant had an acute aleukemic episode, seemingly recovered, appeared well a year and then died with acute leukemia. Autopsy showed widespread leukemic infiltration.

Our finding of haploid mitotic figures only in myeloblasts identifies that cell type as the leukemia cell.[12] The presence of many

relatively mature basophils with an increasing left shift as the malady progresses may only indicate that for some unknown reason basophilic production has been unduly stimulated. We gain the impression that the large number of basophils is merely an exaggerated expression of what is commonly found in the myeloid leukemias. The fact that this case was carefully studied early by Dr. Pfotzer, and found to be a myeloid leukemia without basophilic increase, supports this contention. In the phase in which we saw the case, with a few noteworthy exceptions to which attention has been drawn, it is a counterpart of the reviewed cases, particularly that of Sabrazès.

We would like to call our case acute myeloblastic leukemia with extreme basophilia but believe the term "basophilic leukemia" should be retained until more complete evidence and confirmation has been presented. One may consider these numerous basophils as the progeny of the leukemia myeloblasts potentially basophilic. They are perhaps too evenly distributed along the ancestral line, too normal in appearance and too mature. There is no "hiatus" such as Naegeli speaks of, no gap. The hiatus is in the neutrophil line. The neutrophilic myelocytes are few and neutrophilic promyelocytes practically absent.

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THE RESISTANCE OF RETICULOCYTES TO HYPOTONIC SOLUTIONS OF SODIUM CHLORID AND OF PLASMA.*

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The variation from normal of the resistance of the red blood cells to hemolysis by hypotonic solutions in conditions in which the number of reticulocytes is increased has led to the belief that in this respect "reticulated" red cells differ from "non-reticulated" red cells. The literature contains many contradictory statements concerning the resistance of reticulocytes. By some authors[1,2,3] the resistance has been thought to be decreased; by others,[4,5,6,7] increased and by still others,[8,9,10,11] not to show any difference from that of adult cells. Such differences in resistance have been thought to be dependent on peculiar types of reticulocytes which appear in different abnormal states. Buckman and MacNaugher,[12] for example, found that reticulocytes from cases of pernicious anemia were less resistant to hypotonic salt solutions than the other cells, whereas those found as a result of hemorrhage were more resistant than the other cells.

The red cell resistance to hypotonic solutions of sodium chlorid in various blood disorders has been described in a previous paper.[13] In the present study the resistance in certain cases in which there was an increase of reticulocytes has been investigated. The conclusions have been derived from two types of experimental data: first, an analysis was made of the relation of the number of reticulocytes to the resistance of the red cells to hemolysis in 100 cases of anemia; second, the actual number of red cells and reticulocytes surviving in progressive dilutions of hypotonic sodium chlorid or plasma was determined in a few selected cases of anemia.

Methods. The resistance studies in hypotonic sodium chlorid were made according to the method recently described[13] in which a 0.1 cc. sample of a 20% suspension of washed red cells in 0.85% sodium chlorid solution was added to each of a graded series of 1 cc. samples of hypotonic sodium chlorid. For other resistance studies 1 cc. of a known suspension (30 or 40%) of red cells in plasma was added to each of a graded series of hypotonic plasma solutions. The plasma was rendered hypotonic by the addition of distilled water. In both methods, after thorough mixing, the tubes of cell suspension were allowed to stand for 1 hour. After a careful resuspen-

* This work was enabled in part by the Charles Sedgwick Minot Fellowship of Harvard University.

sion of the cells, red cell counts and reticulocyte preparations were taken from each tube in quick succession.

The red blood cell counts in the hypotonic sodium chlorid suspensions were made in white blood cell pipettes using dilutions of 1 to 20 or 1 to 10. For the plasma suspensions the counts were taken in red blood cell pipettes in dilutions of 1 to 100 or 1 to 200. The error due to the counting of the red cells and to distribution when such low values are obtained is comparatively large as has been determined previously.[14] The standard deviation, when two chambers of 5 squares each are counted, varies from ±60,000 for a count of 750,000 per c.mm. to ±108,000 for a count of 3,000,000. When the counts were in the vicinity of 100,000 or 150,000, as in the sodium chlorid suspensions, they were made in white blood cell pipettes and the standard deviations were ±7,000 and ±8,000, respectively.

Preparations for reticulocyte counts were made on cover slips upon which a drop of a 0.5% alcoholic solution of brilliant cresyl blue had evaporated to dryness. The dried blood films were counterstained with Wright's stain and at least 1000 red cells counted to determine the percentage of reticulocytes. The counting of reticulocytes on smears made from the more hypotonic solutions is difficult because of the presence among the other cells of shadow cells or hemolyzed cells. Only intact cells containing hemoglobin were counted whether reticulum appeared to be present or not. The standard deviation for one individual counting the reticulocytes (1000 red cells) in 10 consecutive smears taken on capillary blood of 1 patient was ±0.7% at a level of 10.5% reticulocytes. The standard deviation of counting the reticulocytes in 10 consecutive samples taken from a suspension of cells was ±2.6% with a count of 22% reticulocytes. The mixing of the sample introduces another error to the simple counting of reticulocytes.

Results. The results of 100 resistance observations are presented in Chart I. This group includes 38 observations in 19 cases of hypochromic anemia, 38 in 19 cases of pernicious anemia before treatment and in 2 cases during the response of the reticulocytes to potent therapy, and 24 in 15 cases of hereditary or acquired hemolytic jaundice. The absolute number of reticulocytes is plotted as abscissa against the minimum resistance or trace of hemolysis and against the maximum resistance or complete hemolysis as ordinate. Chart I shows no evident relation between the number of reticulocytes and the minimum or the maximum resistances, although the number of reticulocytes varied from normal values (under 50,000) to 800,000 per c.mm. If the reticulocytes were responsible for the decrease from the normal minimum or the increase from the normal maximum resistance some correlation should appear. Studies of this kind show no constant relationship between the number of reticulocytes and the resistance to hemolysis of the total cell population.

An attempt was made to determine whether the reticulocytes were more or less resistant than the red cells as a whole by determination of the relative proportion of reticulated and non-reticulated cells surviving in successive hypotonic solutions. The results of studies in hypotonic solutions of sodium chlorid are shown in Table 1 and those in hypotonic solutions of plasma, in Table 2.

The red cell resistance has been shown to vary at the time of a reticulocyte response. If the reticulocytes have the same resistance as the adult red cells, the percentage of reticulocytes should be constant in all the hypotonic solutions; if the reticulocytes are more resistant than the red cells, their percentage should be increased in the lower concentrations; and if the reticulocytes are less resistant than the red cells, their percentage should be decreased as the solutions become more hypotonic.

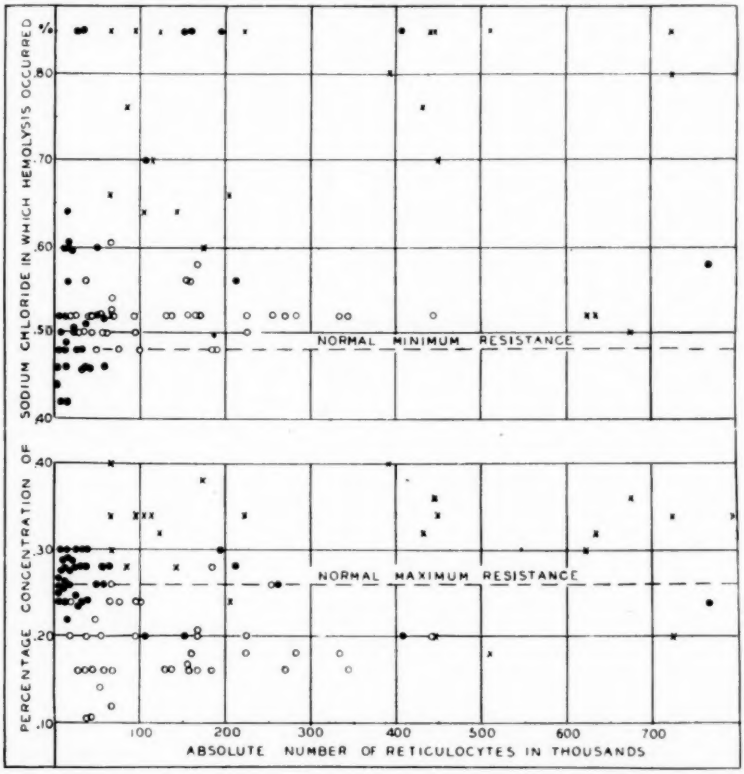

CHART I.—The relation of the absolute number of reticulocytes in 100 observations in anemia to the minimum resistance and maximum resistance of the red blood cells to hypotonic solutions of sodium chlorid.

× 24 observations in hereditary and acquired hemolytic jaundice.
● 38 observations in pernicious anemia.
° 38 observations in hypochromic anemia.

The cells of 3 cases of pernicious anemia (Table 1) were studied before, during, and after the response of the reticulocytes to potent therapy. In Case 1 the percentage of reticulocytes in the hypotonic solutions is practically constant at each of the 3 observations. In Case 2 the percentage of reticulocytes increased in the lower dilu-

tions in the first 2 of the 3 observations. In Case 3, the first observation showed a definite increase of the percentage of reticulocytes in the more hypotonic solutions, and the second observation only a moderate increase in their percentage. Therefore, in certain instances the reticulocytes during remission in pernicious anemia appear to be somewhat more resistant than the red cells as a whole. In the same patient, however, the reticulocytes are apparently more resistant at some times than at others. At times no demonstrable difference between the resistance of the reticulocytes and that of the total red blood cell population can be ascertained by this method.

TABLE 1.—COMPARATIVE RESISTANCE OF RED BLOOD CELLS AND RETICULOCYTES TO HYPOTONIC SOLUTIONS OF SODIUM CHLORID. THREE CASES OF PERNICIOUS ANEMIA.

CASE 1.

NaCl, %	Three Days Before Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	At Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	Three Days After Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %
0.85	0.118	13,216	11.2	0.161	...	..	0.111	9,768	8.8
0.80	0.117	...	..	0.172	41,624	24.2	0.112	10,080	9.0
0.70	0.124	...	..	0.177	49,206	27.8	0.128	...	..
0.60	0.127	...	..	0.163	50,204	30.8	0.115	9,430	8.2
0.50	0.127	16,830	13.2	0.126	27,216	21.6	0.137	10,960	8.0
0.40	0.080	13,524	16.8	0.101	28,684	28.4	0.053	4,399	8.3
0.36	0.046	7,636	16.6	0.052	15,600	30.0			

CASE 2.

	Two Days Before Peak of Reticulocyte Response.			At Peak of Reticulocyte Response.			Two Days After Peak of Reticulocyte Response.		
0.85	0.093	..	..	0.129	22,446	17.4	0.110	16,610	15.1
0.80	0.103	...	..	0.118	25,606	21.7	0.114	...	..
0.70	0.091	11,102	12.2	0.105	17,850	17.0	0.097	16,380	16.8
0.60	0.083	7,765	9.3	0.104	21,528	20.7	0.116	15,080	13.0
0.50	0.100	9,045	9.0	0.105	20,475	19.5	...	...	..
0.40	0.062	6,820	11.0	0.104	21,008	20.2	0.057	7,809	13.7
0.34	0.023	2,890	12.3	0.027	10,807	39.3	...	...	..
0.32	0.013	3,159	23.4						

CASE 3.

	Two Days Before Peak of Reticulocyte Response.			At Peak of Reticulocyte Response.		
0.85	0.141	12,690	9.0	0.118	17,736	15.2
0.80	0.140	...	..	0.102	20,196	19.8
0.70	0.125	17,000	13.6	0.104	19,760	19.0
0.60	0.134	16,080	12.0	0.106	20,908	19.8
0.50	0.119	15,232	12.8	...	...	..
0.40	0.107	15,408	14.4	0.094	14,776	15.4
0.36	0.033	8,710	26.0	0.039	6,630	17.0
0.32	0.017	5,678	33.4	0.019	4,446	23.4

In Table 2 are presented the results of determination of the reticulocyte resistance in various conditions with increased numbers of reticulocytes. In 3 observations on 2 cases of pernicious anemia the percentage of reticulocytes increased in the lower saline dilutions while in 2 other cases the percentage of reticulocytes was quite constant. These results suggest similar conclusions in regard to the resistance of reticulocytes to those drawn from the observations in Table 1.

Two sets of observations on the blood of a case of acquired hemolytic jaundice, which contained from 20 to 68% reticulocytes over a period of 4 months showed an opposite tendency. In both exper-

TABLE 2.—COMPARATIVE RESISTANCE OF RED BLOOD CELLS AND RETICULOCYTES TO HYPOTONIC SOLUTIONS OF PLASMA.

Hypotonic dilutions of plasma, %	PERNICIOUS ANEMIA. CASE 1. At Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	CASE 2. At Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	CASE 3. Day Before Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	CASE 3. At Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	CASE 4. Day Before Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %
100	0.975	133,575	13.7	0.987	205,296	20.8	1.190	202,300	17.0	1.077	186,321	17.3	1.020	108,120	10.6
90	...	....	..	0.952	257,040	27.0	1.040	189,280	18.2	1.157	196,690	17.0	1.040	97,760	9.4
80	...	....	12.5	1.070	287,830	26.9	0.950	161,500	17.0	1.060	181,260	17.1	0.980	105,840	10.8
70	...	....	..	1.000	251,000	25.1	0.980	167,580	17.1	1.120	199,360	17.8	1.070	103,790	9.7
60	0.935	120,615	12.9	0.890	218,940	24.6	1.090	179,850	16.5	1.090	188,570	17.3	1.030	122,570	11.9
55	1.000	124,000	12.4	0.870	214,020	23.6	...	....	..	...	....	..	0.905	99,550	11.0
50	0.820	95,940	11.7	...	....	..	0.790	146,150	18.5	1.070	189,390	17.7	...	....	..
45	0.710	78,810	11.2	0.800	228,000	28.5	0.745	132,610	17.8	0.750	136,500	18.4	0.905	100,455	11.1
40	0.415	48,555	11.7	0.555	158,730	28.6	0.620	128,960	20.8	0.695	164,715	23.7	0.810	83,430	10.3
35	...	....	22.5	0.280	73,640	26.3	0.063	21,621	33.0	...	....	..	0.430	49,450	11.5
	ACQUIRED HEMOLYTIC JAUNDICE—CASE 1. April 20,1934.			April 24, 1934.			HEREDITARY HEMOLYTIC JAUNDICE.			ARSENIC POISONING.					
100	0.840	287,280	34.2	1.120	462,560	41.3	...	....	..	1.330	53,200	4.0			
80	0.920	306,360	33.3	1.180	443,680	37.6	1.680	149,520	8.9	1.250	51,250	3.0			
70	...	....	..	0.785	306,935	39.1	...	....	..	...	....	..			
60	0.710	230,040	32.4	0.985	308,305	31.3	1.860	161,820	8.7	1.350	62,100	4.6			
55	...	....	..	...	....	..	1.760	183,040	10.4	...	....	..			
50	0.592	121,360	20.5	0.660	201,300	30.5	1.685	190,485	11.3	1.110	45,510	4.1			
45	0.152	25,773	16.9	...	....	..	1.560	176,280	11.3	0.867	36,414	4.2			
40	0.045	5,220	11.6	0.135	30,240	22.4	0.770	67,760	8.8	0.565	27,120	4.8			
35	...	....	..	...	....	..	...	....	..	0.235	9,165	3.9			
	ERYTHROBLASTIC ANEMIA.			HYPOCHROMIC ANEMIA.			ACUTE BLOOD LOSS.			RABBIT 1. REPEATED BLOOD LOSS.			RABBIT 2. REPEATED BLOOD LOSS.		
100	2.780	230,740	8.3	2.170	235,445	10.8	...	....	..	1.270	158,750	12.5	1.400	145,600	10.4
90	...	....	..	...	....	..	...	....	..	1.380	171,120	12.4	...	....	..
80	2.940	255,780	8.7	2.020	208,060	10.3	...	....	..	1.580	199,080	12.6	1.220	120,780	9.9
70	2.680	233,160	8.7	...	....	..	...	....	..	1.320	142,560	10.8	...	....	..
60	2.320	160,080	6.9	2.315	203,720	8.8	...	....	4.8	1.400	147,000	10.5	1.380	139,380	10.1
55	...	....	..	...	....	..	...	....	..	1.400	179,200	12.8	...	....	..
50	2.070	184,230	8.9	1.745	148,320	8.5	2.090	89,000	4.3	1.295	175,000	14.0	1.240	128,960	10.4
45	...	....	..	...	....	..	...	....	..	0.825	100,650	12.2	0.875	87,500	10.0
40	1.935	150,930	7.8	1.255	99,145	7.9	1.125	36,000	3.2	0.552	71,760	13.0	0.095	11,495	12.1
35	1.350	116,100	8.6	0.700	52,500	7.5	0.850	34,000	4.0	0.095	11,020	11.6	0.047	....	..
30	1.195	109,940	9.2	0.170	21,250	12.5	0.570	21,660	3.8	...	....	..	...	....	..
25	1.100	....	..	...	....	..	0.245	6,860	2.8	...	....	..	...	....	..

iments the percentage of reticulocytes was very definitely decreased in the more hypotonic solutions, *i. e.*, they were less resistant than the red blood cell population as a whole.

In 1 case each of hereditary hemolytic jaundice, arsenic poisoning, erythroblastic (Cooley's) anemia, hypochromic anemia, and acute blood loss, and in 2 examples of repeated blood loss in rabbits the percentage of reticulocytes remained quite constant in the lower dilutions of hypotonic plasma. Apparently there was no striking difference between the resistance of the reticulocytes and that of non-reticulated cells in this last group of cases studied.

Discussion. There are many sources of error in counting reticulocytes in hypotonic solution which may be responsible for the divergent results of many investigators. When hemoglobin is removed from the red cell by hemolysis a shell or shadow form remains. The reticulum-like material, stained with brilliant cresyl blue, persists, so that the first impression in looking at the cells in the sediments of hemolyzed blood is that none of the reticulocytes has been hemolyzed. This may account for the conclusions in the early work of Chauffard and Fiessinger[15] that reticulocytes were more resistant than the other cells.

Key[10] pointed out that the laked cells floated above the non-laked cells in the sediments in hypotonic solutions. Sampling the top layer, he indicated, might have led to the erroneous conclusion of certain investigators that the reticulocytes were more resistant than non-reticulocytes. When the sediments were thoroughly mixed no constant difference could be observed between reticulocytes and non-reticulocytes in respect to their resistance.

Some investigators[7] have employed a method in which salt solutions containing cresyl blue in solution were used. With "high dry" magnification or in fresh preparations, it is difficult to distinguish in the counting chamber the reticulocytes that have been laked from those that have retained their hemoglobin. Moreover, the oldest reticulocytes, which have only a small amount of punctate reticulum[16] cannot be discerned under "high dry" power and therefore a smaller number of reticulocytes is counted than is actually present.

Buckman and McNaugher[12] report experiments with defibrinated blood incubated at 37° C. for 12 hours. The decrease in the number of reticulocytes at the end of 12 hours, which is interpreted as evidence of decreased cell resistance, is no more than could be expected by the normal maturation of these young cells.[16]

Many conclusions in regard to the resistance of red cells have been drawn from the coincident occurrence of reticulocytes and diminished resistance or increased resistance to hemolysis. The early work of Chauffard[1] assumed that since reticulocytes were increased and resistance was decreased in hemolytic jaundice there was a relationship. Cathala and Daunay[2] found increased reticulocyte counts and diminished resistance of red cells in infants at

birth, and came to similar conclusions. Other observers correlated increased resistance of the red blood cells with the increase of reticulocytes after repeated venesections.[4,5]

Meulengracht[11] concluded from microscopic studies of reticulocytes in fresh preparations from the blood of patients with hemolytic jaundice that there was no relation between the number of reticulocytes and the red cell resistance.

It has been shown[13] that alteration of both maximum and minimum resistance may take place simultaneously in the same patient at the time of a reticulocyte response to either iron or liver therapy. This alteration, however, may be due to factors not necessarily confined to the reticulocytes. Changes in hemoglobin content, volume of cells, and shape of the cells are known to take place at this time, as well as chemical and physical factors which are less easy to measure. Thus the heterogeneity of the cell population is increased not only in respect to age but also in respect to the physical and chemical properties of the cells. In experimental and clinical hypochromic anemia, the volume, thickness and hemoglobin content of the cells are decreased. Under these circumstances, regeneration of blood in response to iron therapy may be accompanied by the appearance of reticulocytes which contain less than normal amounts of hemoglobin. On the other hand, reticulocytes in some conditions, such as hereditary hemolytic jaundice, may be small and full of hemoglobin. Thus differences in resistance of reticulocytes do not seem to be due to any property peculiar to the reticulocytes as such (*e. g.*, because they are young cells), but may be due to fundamental changes in the hemopoietic system during regeneration of blood which may at times affect mature cells as well as immature cells.

Conclusions. 1. The absolute number of reticulocytes observed in 100 cases of pernicious anemia, hypochromic anemia, and hereditary or acquired hemolytic jaundice showed no consistent effect in altering the minimum resistance or maximum resistance of the total red blood cell population to hypotonic sodium chlorid solutions.

2. Actual enumeration of the relative numbers of reticulocytes and red cells surviving in progressive series of hypotonic solutions of sodium chlorid and of plasma showed that, irrespective of the disease present, in some bloods the reticulocytes were more resistant, in some equally resistant, and in some less resistant than the red blood cell population as a whole in the cases studied.

3. Reticulocytes as well as non-reticulocytes vary in age, volume, thickness, hemoglobin content, and probably other physical and chemical properties in the same individual at different times, and in different individuals with varied disease conditions. Thus the fact that young cells are reticulocytes does not necessarily determine their behavior in hypotonic solutions. The reticulocytes may or may not exhibit divergence from the resistance of the cell population as a whole. Such variations may be responsible for the diverse

opinions of other observers in regard to the resistance of reticulocytes to hypotonic solutions of sodium chlorid and plasma.

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SICKLE-CELL ANEMIA: A NEW CAUSE OF COR PULMONALE.

REPORT OF TWO CASES WITH NUMEROUS DISSEMINATED OCCLUSIONS OF THE SMALL PULMONARY ARTERIES.

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THE history of joint pains, with or without fever, the presence of an enlarged heart, the finding of a systolic precordial or mitral murmur and the discovery of enlargement of the liver frequently

lead to the diagnosis of rheumatic heart disease in cases of sickle-cell anemia. According to Anderson and Ware a cardiac murmur is present in 75% of the cases, enlargement of the liver clinically in 53% and enlargement of the heart clinically in 48%. Joint pains occur at some time, often intermittently, in 51%. Dyspnea, however, is usually not a prominent symptom, but it is common experience that effort dyspnea is difficult to elicit in the histories of many Negro cardiac patients. Hamman has reported an interesting case of a Negro girl with sickle-cell anemia in which several excellent clinicians made the diagnosis of rheumatic heart disease, with failure, which was not verified by necropsy. Diggs and Ching state that "Clinically, organic heart disease is often suspected, but at autopsy there are no constant cardiac changes except those explainable on the basis of anemia. The heart is moderately enlarged, the myocardium pale and flabby. On microscopic examination fatty degeneration and moderate scarring are noted." These authors and Steinberg note that the liver is consistently moderately enlarged and the sinusoids distended with varying amounts of blood and that the lining endothelial cells frequently contain brown granules, good evidence of congestion as well as blood destruction.

Although many patients with sickle-cell anemia die at a relatively early age of some intercurrent infection, particularly pneumonia and pulmonary tuberculosis, a fair number die apparently as the result of the anemia itself. It is our belief that cardiac failure is often a part of the terminal picture, as evidenced by enlargement and dilatation of the heart and passive congestion of the liver. Our experience with 2 cases leads us to believe that there is usually something other than the severe anemia producing the cardiac failure, namely, hypertension of the lesser circulation due to numerous occlusions of the medium-sized and small pulmonary arteries with subsequent hypertrophy and failure of the right heart.

Case Reports. Case 1.—H. P., a Negro woman, aged 38 (?), entered the Georgetown University Hospital on February 19, 1935, complaining of dyspnea and swelling of the abdomen. She had attended the Out-Patient Department from August 13, 1934, to October 20, 1934. During that period of observation she had had no definite complaints—was merely not feeling well. She had had attacks of numbness of the feet and pains in the legs, but these had not occurred for several months. She did not recall any previous illnesses except ulcers of the legs some 10 years before which had healed after a long time. Menstruation had begun at the age of 12 years and had been regular but scanty until 3 years before, when it had ceased. She had been married 5 years but had never been pregnant. There was moderate leukorrhea. There were no cardiovascular, respiratory, urinary or other functional disturbances, except "eye strain," for which she had received treatment at the Episcopal Eye, Ear, Nose and Throat Hospital. Physical examination in the Out-Patient Department had been negative except for conjunctival pallor; bad dental condition; a firm, diffuse, freely movable mass in the right breast and smaller discrete masses in the left breast; a systolic apical murmur and a questionable presystolic rumble. The blood pressure had been 120 systolic and 80 diastolic. Urinalysis

showed 1+ albumin and 3+ leukocytes. Wassermann and Kahn tests of the blood were negative. The hemoglobin was 54% (Sahli method), the erythrocytes numbered 1,850,000 per c.mm. of blood and the white blood cells 8200. There was great variation in the size and shape of the erythrocytes but there were no definitely sickle-shaped cells in the fresh smear. After incubation of a wet smear overnight there were numerous fusiform, stellate-shaped and sickle-shaped erythrocytes characteristic of sickle-cell anemia. The patient was urged repeatedly to enter the hospital but would not do so until the onset of the final episode of her life.

On admission to the hospital the patient stated that 3 days before severe dyspnea had begun, associated with swelling of the abdomen. Both symptoms progressed rapidly.

Physical examination revealed a well developed and nourished orthopneic Negress. The ocular fundi were essentially normal. The conjunctivæ and buccal mucous membranes were pale. Cyanosis was not present. There was much dental work and some pyorrhea. The cervical veins were markedly distended, pulsated and filled from below as well as from above. The breasts contained the masses already noted, but the large one in the right breast was now fixed to the skin and the nipple was retracted. Moderately enlarged, firm lymph nodes were palpable in the right axilla. There was dullness in the right hemithorax posteriorly up to the fourth interspace. The breath sounds were exaggerated in the interscapular space. There were no râles. The point of maximum intensity of the apex beat was easily determined to be in the sixth interspace, 11 cm. to the left of the midsternal line (clavicle, 15 cm.). There was a harsh systolic murmur over the precordium, loudest at the apex, and a questionable diastolic murmur at the apex. The heart shifted with change of position. The rhythm was regular and the rate 100 beats per minute. The blood pressure was 105 systolic and 60 diastolic. The abdomen was very prominent in its upper portion, due to great enlargement of both lobes of the liver, which extended about 7.5 cm. below the costal margins. There was apparently no ascites. There was no edema of the legs. Ulcers were noted on both legs. The temperature was 100° F.

The hemoglobin was 52% (Newcomer method), the erythrocytes numbered 2,500,000 per c.mm. of blood and the white blood cells 11,400, with 86% neutrophils. There was marked anisocytosis and poikilocytosis. Urinalysis showed 4+ albumin and 2+ hyalin casts. A roentgenogram showed great enlargement of the heart, both to the right and left, with a bulge in the region of the pulmonary conus and widening of the superior mediastinal shadow on the right and left, due apparently to engorgement of the great veins. There was some mottling of the lung fields, suggesting mild congestion (Fig. 1).

The temperature dropped to normal and remained so. The pulse rate became stabilized at 90 beats per minute. The orthopnea continued. Subcrepitant râles appeared at the bases of both lungs posteriorly. On the night of February 21 the patient became wildly excited and complained of great pain in the sacral region and some in the lower abdomen, relieved by a hypodermic injection of morphin sulphate, 0.011 gm. ($\frac{1}{6}$ grain). The blood pressure at this time was 100 systolic and 50 diastolic. Slight edema of the ankles developed. Death occurred at 7.40 A.M., February 22, 1935, 66 hours after admission and 5 days after the apparent onset of the right heart failure.

Necropsy Report. The postmortem examination was performed by Dr. Hansmann on the unembalmed body, the same day at 11.00 A.M. The body was that of a well developed and nourished Negress, 155 cm. in length, with delicate tapering hands and feet. There was no rigor. The eyes were prominent and practically protruded from the sockets. The small venules

of the conjunctivæ and scleræ stood out prominently, giving these structures a dusky appearance upon a yellowish background. The pupils were round and equal and measured 0.4 cm. in diameter. The conjunctivæ, nail beds and mucous membranes were cyanosed and icteroid. The veins of the neck were markedly distended, even the small veins of the scalp standing out prominently. There was no demonstrable edema. There were chronic ulcers laterally over the left ankle and over the right tibia. The right nipple was fixed to the underlying breast, and the breast, which was firmer than normal, was fixed to the underlying structures. The skin about the nipple was thickened and wrinkled and contained a few miliary nodules. The right upper quadrant was particularly hard and a poorly defined mass was felt. The right axillary lymph nodes were hard and enlarged up to 1.5 cm. Section of these structures revealed gray granular tissue characteristic of carcinoma. The left breast was uniformly firm. Cut section revealed resilient white scar tissue and a few cysts 1 cm. in diameter containing a bluish fluid. The left axillary lymph nodes were enlarged up to twice normal size but were not hard. The fat over the chest and abdomen was very edematous and measured 0.75 cm. and 3 cm. in thickness respectively.

On opening the thorax and abdomen, the serous cavities, with the exception of the left pleural cavity, were found to contain an excess of watery fluid. The pericardial cavity contained about 100 cc., the right pleural cavity about 200 cc., and the peritoneal cavity about 500 cc. The omentum was adherent to the anterior abdominal wall. The uterus, tubes and ovaries were infantile.

The mediastinum was markedly widened by a heart that was much more dilated than hypertrophied. It pushed the lungs aside. The right auricle participated in this widening of the mediastinum quite as much as the ventricles, and the right lung was obscured as much as the left. The superior and inferior venæ cavæ were markedly dilated. The opened heart, free of all blood clot, weighed 350 gm. The left ventricle was slightly dilated and hypertrophied. The right ventricle was very much dilated and hypertrophied, its wall measuring 0.4 cm., while that of the left measured only 1.2 cm. More important than these measurements was the tremendous thickening of the intracardiac muscle structures. They gave the interior of the heart a coarse, trabeculated appearance. The pulmonary valve orifice was about 1 cm. larger than normal in circumference. Other valve orifices appeared unaffected. The musculature of the right auricle was somewhat hypertrophied, especially when one considered the marked increase in the size of the cavity. The aorta contained a few young atheromatous plaques. The main pulmonary arteries were smooth, and the coronary arteries were apparently normal.

The lungs were edematous, and there was definite bleeding into the alveoli of the lower lobes. There was no gross area of infarction. When the lungs were sectioned, however, many thrombi in various stages of organization were seen in the small and medium-sized arteries. These vessels were evidenced by firm cylindrical structures from 1 to 2 mm. in diameter which varied from granular recent red blood clot to the pearly white glistening appearance of a fully organized thrombus. An individual thrombus involved several millimeters of a vessel that appeared normal elsewhere. This process was diffusely scattered throughout all lobes. The obstruction offered by these thrombi must have been great when one considered the facts that many occurred in a single section and that the length of the individual thrombi was but a few millimeters.

The spleen was markedly contracted and finely granular. The surface was reddish-white. It weighed 7 gm. On cut section the pulp was very gritty and had a distinct reddish appearance. The vessels entering and leaving the spleen were normal in size.

The gastro-intestinal tract showed definite edema. The liver weighed 1715 gm. It was acutely swollen, and the margins were blunted. Its color was deep blue streaked with yellow. The cut surface revealed opaque areas stained yellow in the location of the central veins. This indicated extensive central necrosis with dead cells stained with bile. The gall bladder was shrunken and thickened, and the cavity contained many pigment stones.

The right kidney weighed 200 gm, and the left 210 gm. They were somewhat globular, firm and red from passive congestion. The cut surface showed shrunken areas with underlying scars having the configuration of ancient small infarctions. The intervening kidney cortex appeared normal except that the glomeruli were about twice normal size and intensely congested. Near the apex of the pyramids the renal substance had a white glistening appearance which had the toughness of scar tissue. There was no visible atheroma of the larger arteries, but there was some thickening of the smaller arteries. The adrenals were normal in size and architecture. The urinary bladder was normal.

The brain weighed 1365 gm. The surface appeared normal grossly except that there had been some recent diapedesis of red blood cells into the meninges over the right hemisphere. Coronal sections were made. There was a small area of softening 1 cm. in diameter in the left parietal cortex. The choroid plexus was uniformly shrunken, ashen in color and in places appeared as a white cord. Upon exposing the spinal canal, a fibrinous plaque 1 cm. in diameter was noted upon the dura in the lumbar region posteriorly. Gross serial sections of the cord revealed small petechiæ in the nerve trunks as they emerged from the cord to enter the dorsal root ganglia in the dorsal and lumbar regions. The posterior root ganglia appeared normal. The pituitary gland was not abnormal.

The bone marrow from the upper one-fourth of the femur was gelatinous and had the appearance of edematous fat. It was distinctly gritty and necessitated decalcification before a section could be made.

Microscopic examination of the formalin-fixed tissues revealed the following: The muscle fibers of the myocardium were fragmented and somewhat granular. Some of the very thin-walled vessels were distended, giving the appearance of pools of blood. The smaller arteries were definitely tortuous and the walls were hyalinized. The knuckling of these vessels caused the vessel to be cut across as many as 4 times in the same plane.

Six sections taken from various parts of the lungs were studied. All showed occlusion of small arteries which had been stretched before they became occluded. The occlusions varied from recent thrombi to completely organized and canalized thrombi (Fig. 2, 3, 4, 5). Some small arterioles were thickened and hyalinized, while others were tremendously dilated and distended with blood. The alveolar walls were markedly lengthened, due to the extreme stretching of their capillaries by erythrocytes. The parenchyma had the appearance of most extreme passive congestion. Many areas appeared angiomatous because of the frequent cross section of lengthened snarled capillaries. The red blood cells contained in these vessels had a bizarre appearance. The characteristic forms were very long and had a digital arrangement. Many times the space between these elongated parallel cells was obscured and the appearance was then that of a hyalin thrombus of capillary size. A few of the thickened arteries had collections of hemosiderin in their walls, the consequence of old small hemorrhages. There were 3 small areas of recent infarction.

Section of the spleen necessitated decalcification. The section revealed a mass of hyalinized scar tissue which contained many occluded large and medium-sized arteries. There was still some of the intense blue color in the walls of some of the vessels characteristic of calcium incrustation. The

few vessels which had remained patent were closely packed with cells of almost every shape described in sickle-cell anemia.

Four sections of the liver were studied. The liver cords were markedly thinned. The sinusoidal spaces were dilated. Large areas appeared as a cavernous angioma filled with sickle cells, the intervening liver cells having disappeared from pressure atrophy. A large area about the central vein showed marked hepatic-cell injury and necrosis. The dead liver cells were hyalin. Neutrophils were in abundance digesting the dead cells. Injured cells were swollen and vacuolated. Small bile ducts were plugged with inspissated bile. There was abundant hemosiderin pigment in both the hepatic and Kupffer cells. Vessels entering the lobule from the periportal space were tortuous. No intact red blood cells were seen within Kupffer cells.

The pancreas was normal.

The kidneys were markedly diseased. Fourteen sections were studied from various parts. Near the apex of the pyramids and extending quite deeply into the kidney substance were plaques of dense hyalin scar tissue which appeared like cartilage. The rich network of capillaries had been destroyed, and the tubules traversing the scar had atrophied. The glomeruli were large and distended with sickle cells. Some of the cells were so closely packed that they appeared agglutinated and resembled hyalin thrombi. Small granules of hemosiderin were numerous in the endothelium of the glomerular tufts. There were many scars in the cortex. Many glomeruli were partially and completely sclerosed. Arterioles entering these areas were thickened and tortuous. The sclerosed glomeruli frequently had streaks of hemosiderin in them. It appeared that the glomeruli had become sclerosed while they were distended with blood. The lining cells of the convoluted tubules contained a great deal of hemosiderin.

Section of the breast revealed a scirrhous carcinoma, and the lymph nodes in the axilla were replaced by a mass of medullary glandular epithelial tissue. The lymph nodes from the bifurcation of the trachea were tuberculous. The axillary lymph nodes from the left axilla were hyperplastic. The endothelial cells of the sinuses contained hemosiderin, but no intact phagocytosed sickle cells were seen.

The bone marrow was made up largely of hyalin connective tissue similar to that seen in the kidney and spleen. It was necessary to decalcify this tissue before a section could be made. The section contained only a few small spicules of bone. It would appear that most of the calcium which the fresh tissue contained was incrusted calcium rather than calcium laid down in bone matrix in the normal process of ossification. Along one margin was a thin staff of active bone marrow. Between the hematopoietic cells were large pools of sickled cells.

A section of the aorta appeared normal.

The cortex of the brain revealed meningeal vessels distended with blood. A few sections showed a thin layer of diapedesed blood over the surface of the cortex. The vessels were so tortuous that as many as 8 cross sections of the same vessel were seen in a single space. Two vessels had many phagocytes filled with hemosiderin about them. There was 1 small area of recent softening. In the marginal zone of the cortex were many large mononuclear cells filled with a reddish-brown pigment. The choroid plexus was practically sclerosed and was markedly incrusted with calcium (Fig. 6). The lesion here was similar to the lesion in the spleen. The pituitary gland appeared normal. The cord showed a small hemorrhage into the meninges in the lumbar region. A nerve cell in the anterior horn was in the process of degeneration. About it was an area of edema and hemorrhage. The cord contained diffusely an unusual number of corpora amylacea, which were particularly numerous in the posterior

columns. There was an area of hemorrhage on the inner surface of the dura. The vessels in the nerve trunks were packed with sickle cells.

In view of the interesting findings in Case 1, and recalling the enlargement of the liver in the case previously reported by Yater and Mollari, we reviewed that case from the standpoint of pulmonary vascular lesions and the right side of the heart. A brief abstract of the history follows.

Case 2.—S. C., a Negro woman, aged 25, entered Georgetown University Hospital on November 18, 1929, because of severe pains in both legs. She was about 6 months' pregnant. She had had these pains in the legs intermittently since early childhood. At the age of 14 she had been operated on in the hospital for an "osteomyelitis" of the distal third of the left tibia. Two years before she had entered the hospital because of bleeding following a miscarriage at 6 months. At this time she was very ill and had a septic temperature for 7 weeks. Her hemoglobin went as low as 12%, with 950,000 erythrocytes per c.mm. Following this illness she had never been strong and was always dyspneic on exertion.

On the last admission her temperature was 101° F., and the pulse 120 per minute. The blood pressure was 115 systolic and 65 diastolic. The heart was slightly enlarged to the left, the apex beat was diffuse, and a soft systolic murmur was heard at the apex. The liver was not palpable. There was no evidence of congestion. Blood examination showed 44% hemoglobin (Dare method), 2,570,000 erythrocytes per c.mm., and 14,800 white blood cells per c.mm. Sickling was seen in fresh smears. Wassermann and Kahn tests of the blood were negative. The electrocardiogram showed only sinus tachycardia.

The patient was in the hospital 6½ weeks until her death, with practically continuous and excruciating pains in the legs. The temperature fluctuated, but usually each day it rose to a point never over 101° F. The pulse rate varied continuously between 100 and 140 beats per minute. After 3½ weeks the patient miscarried spontaneously. Eighteen hours before death she suddenly vomited and began to complain of severe pain in the right side of the abdomen anteriorly and mainly in the region of the liver. A resistance was felt in the upper half of the abdomen suggestive of enlargement of the liver, which had not previously been noted. The pain continued until death, the pulse rate and temperature steadily falling.

Necropsy Report. There was edema, Grade 2, over the tibias. Cyanosis was not present. A small amount of clear, straw-colored fluid escaped when the abdominal cavity was opened. The liver was seen to fill the whole upper half of the abdomen, reaching below the costal margin in the right midclavicular line 14.5 cm., in the left midclavicular line 12 cm., and in the median line 18.5 cm. below the tip of the xiphoid process.

The pericardial sac measured 15.5 cm. in its transverse diameter and contained about 125 cc. of clear, straw-colored fluid. The heart weighed 379 gm. All cavities were distended with blood. The right ventricle was dilated Grade 3, the left Grade 2. The tricuspid orifice admitted 4 fingers, the mitral orifice 3. The right ventricle was definitely hypertrophied. The thickness of the left ventricle was 1.2 cm. in its mid portion, the right 0.55 cm. The muscle was reddish-brown and fairly firm. The endocardium and valves appeared normal. The aortic orifice measured 5 cm. in circumference, the pulmonic 7 cm. The coronary arteries were soft.

The lungs were emphysematous, Grade 2, in both upper lobes. Nothing otherwise notable was recorded except an area of bronchiectasis. They were not saved.

The spleen weighed 35 gm. and was typical of advanced sickle-cell anemia.

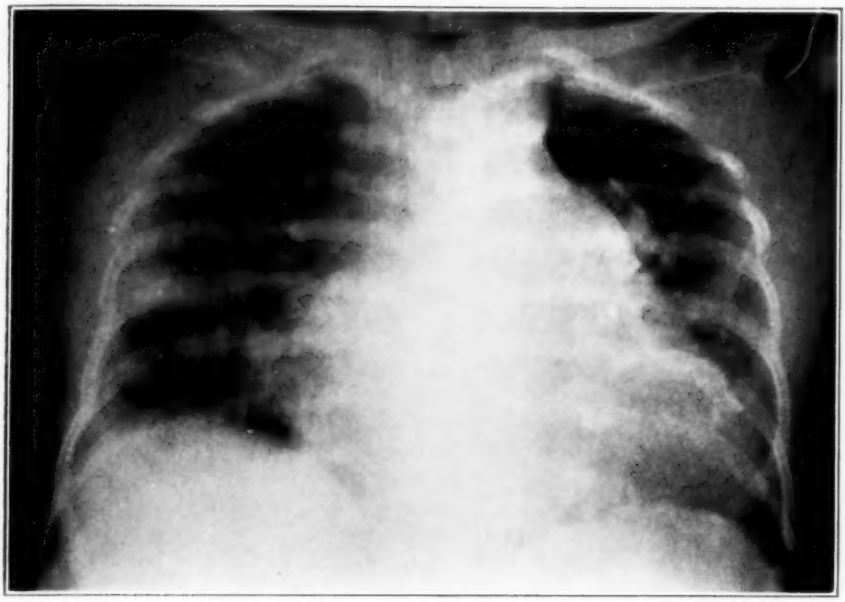

FIG. 1.—Case 1. Greatly enlarged heart with bulge in the region of the pulmonary artery and widening of the superior mediastinal shadow due to venous engorgement.

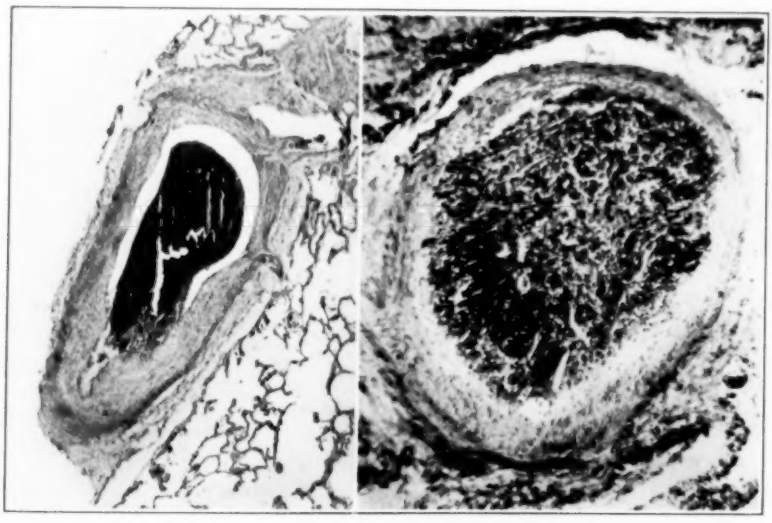

FIG. 2 FIG. 3

FIG. 2.—Case 1. A medium-sized pulmonary artery containing a recent thrombus which is undergoing organization at one point. (× 70.)

FIG. 3.—Case 1. A small pulmonary artery filled with an organized thrombus. (× 215.)

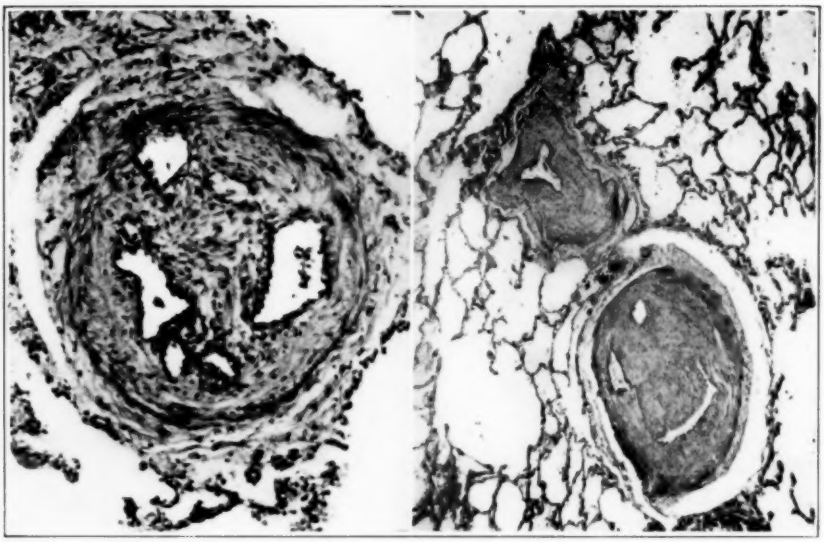

FIG. 4 FIG. 5

FIG. 4.—Case 1. A small pulmonary artery completely recanalized. (× 170.)
FIG. 5.—Case 1. Cross sections of a small recanalized pulmonary artery. (× 105.)

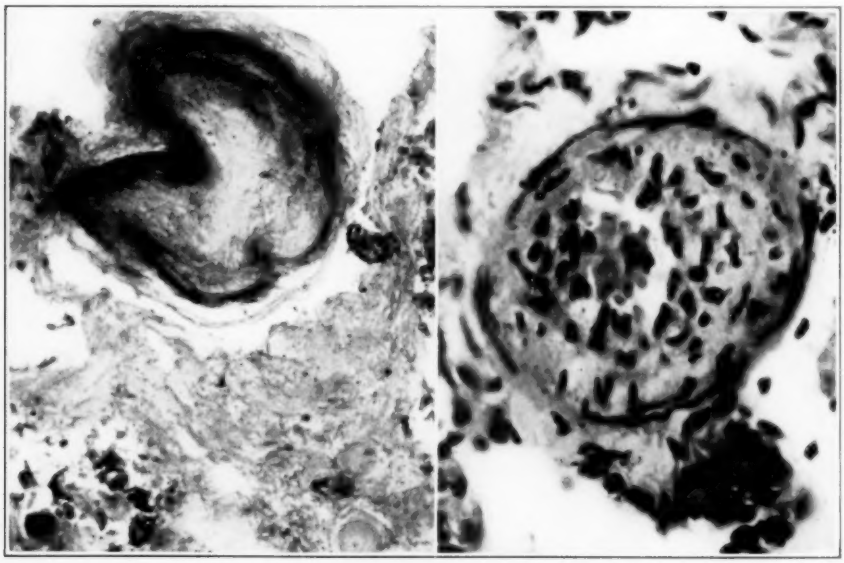

FIG. 6 FIG. 7

FIG. 6.—Case 1. Sclerotic choroid plexus with calcium incrustations. (× 135.)
FIG. 7.—Case 2. A representative arteriole in the lung with a greatly thickened wall, early degenerative changes and a small lumen. (× 1050.)

The liver weighed 2090 gm. It was reddish-brown with distinct yellow mottling throughout. The large veins were entirely empty, but dark clots filled many of the bloodvessels and were practically extruded when the cut was made. The gastro-intestinal tract was not remarkable.

The kidneys presented the same appearance as those of Case 1, but contained some fresh infarcts.

Microscopic examination showed engorgement of the capillaries of all of the organs. The spleen as previously described was the typical spleen of advanced sickle-cell anemia.

The myocardium showed fragmentation of the fibers.

The cords of liver cells were narrower than normal, and the sinuses were distended and in general filled with sickle-shaped erythrocytes. The picture was that of severe congestion. There were small "pools of blood" here and there. A more complete description appears in the report of Yater and Mollari.

The kidneys were similar to those of Case 1.

There was only one section of the lung. This showed engorgement of the capillaries of the alveolar walls, but most interesting were the arteries and arterioles. The medium-sized and small arteries had greatly thickened walls and were apparently quite tortuous. There were no old or recent thrombi in the section, nor was there clear cut evidence of ancient organization and canalization. The arterioles presented the appearance as seen in the arterioles of the kidneys in essential hypertension. There was great hypertrophy of the media with early degenerative changes. The lumens were greatly reduced in diameter (Fig. 7).

In Case 1 the histologic appearance of the medium-sized and small pulmonary arteries was suggestive of non-inflammatory thrombo-angiitis obliterans. Many of the vessels had been the site of a patchy thrombosis which had led to organization and recanalization. Others were in various stages of organization. Many fresh thrombi were present, and it was probably the sudden occurrence of these which caused the right ventricle, already working against obstruction in the pulmonary arterial tree, to fail entirely. We felt that the thrombotic phenomena and their sequelæ of organization and canalization were features of sickle-cell anemia, and our conviction was verified by the discovery of vascular changes in the lungs of Case 2.

In Case 2, although in the tissue material available there were no pulmonary arteries which contained fresh or organizing thrombi, the medium-sized and small arteries showed evidence of ancient changes which were probably due to thrombosis and organization. The arterioles all showed great medial hypertrophy and diminution in the diameter of their lumens. These arteriolar changes were probably secondary to the hypertension in the pulmonary circulation resulting from the obstruction in the medium-sized and small arteries, and may have represented compensatory changes to prevent overdistention of the arterioles. The arterioles were similar to those in the lungs of 2 cases described by Yater and Constam in which sickle-cell anemia did not exist.

In the original report of Yater and Mollari of Case 2 note was not made of the pulmonary vascular changes nor of the hypertrophy

of the right ventricle. The former were recorded in the original protocol but were not regarded as of sufficient importance to comment upon in the published report. The hypertrophy of the right ventricle was overlooked. We feel that the splenic lesions in sickle-cell anemia have been overemphasized and that other authors may have also been overlooking the pulmonary and cardiac lesions.

Cyanosis was not observed during life in either of the cases here reported. In this respect the cases did not present the typical picture of right heart failure known as Ayerza's syndrome. There is a striking difference, however, between the ordinary case of Ayerza's syndrome and the cardiac picture in sickle-cell anemia, namely, that in the one there is polycythemia and in the other usually severe anemia. Also, the usual case of cor pulmonale due to pulmonary arteriolar sclerosis is one in which dyspnea has occurred for months or years before death. The patient with severe sickle-cell anemia, however, dies usually before he can develop the full-blown picture of chronic right heart failure.

In reviewing the literature on the pathology of sickle-cell anemia we find reference by Steinberg to "marked congestion of the capillaries and the larger vessels (of the lungs) and the presence of serum in some alveoli" as constant observations in 5 cases in which descriptions of the lungs, free of pneumonia or tuberculosis, were given. Steinberg states that "In my patient, the small and medium-sized pulmonary vessels contained fresh or organized blood thrombi with an occasional one canalized, and as a consequence there were fresh and old infarcts. The cause of the thrombosis may have been either the abnormal and weakened myocardium or the tendency of the sickle-shaped red blood cells to agglutinate." Diggs and Ching state that "With the exception of sickled cells and the increased frequency of thrombi and infarcts the lung presents no unusual features. Pneumonia and tuberculosis are frequent."

Thrombotic phenomena are important episodes in the life history of patients with sickle-cell anemia. The organ most severely affected is the spleen. In a personal communication Diggs states that "Obliterative vascular changes and thrombi are surely a part of the pathological picture of sickle-cell anemia. We have observed organized and multiple thrombi in the lungs and in the spleen. The leg ulcers probably have thrombosis as part of their mechanism, and the patchy bone changes are those that would be associated with circulatory stasis. I have not noticed arteriolar sclerotic processes in the various organs except the spleen, but it is possible that it is generalized. The enlarged hearts these patients have and the maintenance of normal blood pressures in spite of very severe anemia and myocardial degenerative changes speak for peripheral resistance. I have thought that the shape of the cells was the explanation, and that the distorted, elongated forms favored stasis everywhere."

In Case 1 we have noted the same changes in the choroid plexus

as are found in the spleen in advanced cases. The pathology of the nervous system has not been adequately studied, but vascular phenomena have been observed clinically in the form of subarachnoid hemorrhage with cerebral softening in 1 child by Cook, and as hemiplegia associated with other cerebral disturbances in 2 children by Arena. It is possible that the abdominal crises and other pains may be due to vascular disturbances in the nervous system such as we noted in Case 1. Leivy and Schnabel have suggested the possibility of such an origin.

The puckered surface of the kidneys which is so frequently present is undoubtedly due to obliteration of the small arteries. The scars near the apices of the pyramids seem to be due to obliteration of the capillary bed between the collecting tubules. The engorgement of the capillaries of many organs attests the general vascular stasis.

The cause of the tendency to capillary engorgement and arterial thromboses is not definitely known. Diggs' theory that the distorted shape of the erythrocytes prevents their ready passage through the capillaries is probably a large factor in the general vascular stasis, aided by the apparent tendency of the cells to agglutinate. The studies of Scriver and Waugh are confirmatory of the probability that the degree of oxygen unsaturation is a large factor in the amount of sickling *in vivo*. Undoubtedly there is an increase in the degree of sickling *in vivo* from time to time depending upon the degree of capillary stasis and other factors. The amount of sickling seen in fresh blood smears probably does not represent the actual amount of sickling in the circulating blood, since the oxygen content of air tends to restore the shape of the erythrocytes. The study of the 2 cases here reported reveals the fact that the small arteries of practically all organs have been placed under severe prolonged strain, as evidenced by lengthening, tortuosity, hyalinization, hemorrhage into their walls and thrombosis. The site of the greatest stasis and obstruction is undoubtedly the capillary bed, through which the distorted erythrocytes have the greatest difficulty in passing. The burden placed upon the small arteries would explain well the vascular pathology.

Summary and Conclusions. 1. Two cases of sickle-cell anemia with hypertrophy and failure of the right side of the heart have been reported. In one, the heart failure was acute and manifested by orthopnea, great enlargement of the liver and dilatation of the heart. In the other, heart failure was not suspected clinically because of absence of orthopnea, but the liver became greatly swollen. Cyanosis was not present in either in life.

2. The cause of the right heart strain in the first case was thrombotic occlusions of the small and medium-sized arteries of the lungs, with organization and canalization of discrete thrombi which had formed from time to time. The heart failure was apparently precipitated by a final crop of fresh thromboses. The cause of the right heart failure in the second case was thickening of the walls

of the small and medium-sized arteries and the arterioles of the lungs with reduction in their lumens, but thromboses were not present in the tissue studied.

3. The absence of cyanosis is probably explained by the severe anemia, which prevents sufficient concentration of reduced hemoglobin to produce the picture of Ayerza's syndrome.

4. Right heart failure due to vascular changes in the lungs must be common in cases of sickle-cell anemia, since many of the patients have enlarged hearts, systolic murmurs and hepatomegaly.

5. Capillary stasis due to distortion and agglutination of erythrocytes is probably the essential factor in the changes described in the small arteries.

6. Changes in the nervous system are described in the first case, among which are the same lesions in the choroid plexus as are seen in the spleen in cases of advanced sickle-cell anemia.

7. The changes in the bone marrow differed from those previously reported in that they also were similar to those observed in the spleen.

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THE ELECTROCARDIOGRAM IN FEVER.

CHANGES IN INDUCED HYPERPYREXIA.

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The use of hyperpyrexia induced by physical means in the treatment of various ailments, has afforded us the opportunity of studying the changes in the electrocardiogram produced by fever uncompli-

cated by acute infection. Though this subject has considerable practical clinical importance as well as physiologic interest, it has been given little attention. Medical literature contains but few references and they deal almost entirely with animal experiments.[1,2,3,7]

We studied the changes occurring in 10 patients who could not be necessarily regarded as strictly normal[4] from the cardiac point of view, though the physical examination of the heart revealed no abnormalities and the electrocardiogram showed no significant changes. However, 1 case in which the *P–R* interval was prolonged was purposely included. All patients were afebrile.

The systemic temperature was elevated by means of diathermy and photothermy (Bierman[5,6]). The rectal temperature was raised to between 104 to 106.5° F. for a period varying from 3 to 5 hours. The electrocardiograms were taken before the establishment of the fever, at hourly intervals during its maintenance and shortly thereafter. An average of about 10 electrocardiograms were made during each fever session. During the recording, the diathermy current was discontinued and the patient was disturbed as little as possible. In several cases a small dose of a barbital compound had been given.

Rate Changes. With the inauguration of fever, the heart rate increased rapidly. In a previous series[9] of 500 cases it averaged 8.5 beats per minute for each degree Fahrenheit temperature elevation.

Bazett[7] observed in animals, that on the ascent of the fever, at the same temperature, the pulse was usually more rapid than when the fever was on its way down. Our findings were in accord with this. The maximum rate to which the pulse rose was usually between 146 and 162.

Electrocardiographic Changes. *P* wave. The amplitude changes were slight and not always in the same direction. In Lead I, the *P* wave became taller in 5 cases and smaller in 5, the greatest variations were an increase of 1 mm. and a decrease of .4 mm.

In Lead II, the *P* wave amplitude was increased in 3, diminished in 3 and both increased and diminished in 3 cases; in 1 case because of merging with the *T* wave, the *P* wave could not be accurately measured. The maximum variations for Lead II were an increase of 1 mm. and a decrease of .6 mm.

In Lead III, the *P* wave was more often increased in size. There were increases in 7 cases. In 1, the amplitude was diminished and in 2 it was both increased and diminished. Here the maximum change was from −1.4 to +.8, and increase of 2.2 mm.

The width of the *P* wave showed less variation. In most cases, slight changes took place, usually of about .01 to .02 second. In Leads I and II, the duration increased and diminished in an equal number, while in Lead III more were increased (6 to 3). The greatest variation was .04 second, an increase from .04 to .08 second and also a decrease from .07 to .03 second.

The *P–R* interval was diminished in all leads in all cases with one minor exception. It tended to parallel the temperature change. The greatest

reduction was .07 second, from .19 to .12 second. In 1 patient in whom the *P–R* interval was abnormal, .22 second, this interval was reduced to within the normal range during the fever.

Q–R–S. The amplitude of the *Q* wave in Lead I was unchanged in most cases. In 1 it was slightly increased (.7 mm.) and in 2 slightly diminished (.3 mm. and .9 mm.). In Lead II, it was unchanged in 5 cases, slightly increased in size in 3 and showed both increases and decreases in 2 cases. In Lead III, *Q* became deeper in 7 cases in 1 of which (B. M.) it increased sufficiently to fulfill the criteria for "prominent or significant Q_3." Its size was diminished in 1 case and unchanged in 2.

The *R* wave tended to become smaller with the increase in temperature of the patient.

In Lead I, the R amplitude was reduced in 5 cases, in 3 of which it was reduced to the normal borderline of 5 mm. or below. The greatest reduction was one of 6.5 mm., from 17 to 10.5 mm. In only 1 case was it increased.

In Lead II, *R* was decreased in size in 7 cases, in 2 of which it was reduced to 5 mm. or less; the maximum change was 7 mm. (10. to 3.). There was also an increase in 1 case and both increases and decreases in 2.

In Lead III, *R* was reduced in 5, 2 to below the normal borderline of 5 mm. In 2 cases, there were increases, both from below 5 mm. to above. In the remaining 3 cases it was both increased and decreased in each. These effects were not due to changes in the electrical axis which varied little. No slurring was produced.

The *S* wave showed a general tendency to be slightly increased in amplitude in Leads I and III. It was equally slightly increased and decreased in size in Lead II. The maximum variations were 2 to 3 mm. in Leads I and II, and 4.5 mm. in Lead III.

The general tendency for the *Q–R–S* interval was to become diminished as the body temperature rose. The maximum change was .04 second from a duration of .08 second to one of .04 second.

In the few remaining instances, there was either a slight increase in duration or no change at all.

R–T Phase. The *RT* level was depressed by the fever in Leads I and II in almost every case. In no instance was it elevated.

In Lead III, however, it was elevated in 5 cases, depressed in 2 and showed no deviation in 3.

The maximum variation was .6 mm., the usual .3 mm. The *RT* duration was decreased in all cases in Lead I. In Leads II and III it was diminished in 5 each—increased in 3 each, and both increased and decreased in 1 each.

T Wave. The *T* wave amplitude in Lead I had the same incidence of increases as decreases. In Lead II, it was slightly more often increased and in Lead III, much more often increased. The maximum increase was 4.5 mm.; that in Lead III. The maximum reduction was 3 mm., also in Lead III.

In 3 instances, in Leads I and II, *T* was reduced from a normal to an undersized wave, 1 mm. or less. In 2 instances, it was enlarged from a borderline size to one well above.

LEGEND FOR TABLES—LEADS I, II AND III.

The galvanometer is standardized to give an excursion of 1 cm. for 1 millivolt. All amplitude and level displacement measurements are in millimeters. All wave duration and interval measurements are in seconds. The first row for each patient, is the control reading taken before the beginning of temperature elevation. The second row records the maximum change during the temperature elevation; if both an increase and a decrease were present—both are recorded. b = biphasic; M = merged with *T* or *P* wave; * received morphin sulphate gr. ¼. The skin resistance was always between 1000 and 2000 ohms.

Lead I.

	Age.	Highest temp., °F.	Hrs. of 104 or over.	Rate per minute.	P amplitude.	P duration.	P-R	Q	R.	S.	Q-R-S interval.	RT level displacement.	RT duration.	T amplitude.	T duration.	TQ interval.
H. L.:																
Gonococcal arthritis	38	106.1[R]	5.5	72	.8	.10	.16	.3	7.	0.	.06	0.	.14	1.3	.15	.48
				120	1.	.07	.11	0.	3.5	.3	.04	0.	.13	1.	.12	.18
B. M.:		*														
Gonococcal arthritis	36	105.8[M]	3.5	.94	1.5	.07	.16	0.	11.	2.5	.17	0.	.08	2.	.14	.36
				133	2.5	.08	.12	0.	19.	.5	.08	− .5	.04	4.	.18 (.12)	.16
E. H.:																
Multiple sclerosis	44	104.	?	92	1.	.06	.12	0.	11.	0.	.07	0.	.20	− .8	.07	.32
				120	1.2	.08	.11	0.	5.	.8	.06	− .5	.10	− 2 − .3	.09	.24
M. L.:																
Gonococcal arthritis	20	106.1[R]	.5	.67	.7	.08	.16	0.	7.5	1.2	.07	0.	.14	2.	.12	.60
				146	.3	.08	.14	0	4.	3.	.05	0	.08	1.2	.16	.16
M. J.:																
Non-specific infectious arthritis	42	106.8	.5	73	.8	.09	.19	.8	11.	2.	.10	.4	.10	.3	.16	.44
				188	1.4	.07 (.10)	.12	6 (4)	5.5	.2	.07	− .2	.04	1.4	.12	.10
H. H.:																
Non-specific infectious arthritis	20	105.9[M]	.5	104	.6	.08	.14	0.	7.	4.5	.08	0.	.07	2.2	.14	.28
		106.1[R]		122	1.4 (.5)	.10	.13	0.	5. (5.8)	6.5	.08	0.	.03	2.8, 2.0	.12	.24
E. G.:																
Gonococcal arthritis	29	105.5[R]	3.5	86	.8	.08	.13	0.	5.	0.	.08	− .2	.16	1.5	.16	.30
				130	.4	.07	.12	0.	6.5 (4.2)	1.5	.05	− .4	.08	1. (1.6)	.14	.16
*E. H.:																
Gonococcal salpingitis	25	105.7[M]	4.	107	.8	.08	.13	1.7	17.	2.	.09	0.	.07	2.	.15	.24
				143	.5	.06	.08	.8	10.5	0.	.06	− .4	.10	1.	.18 (.22)	.12
*J. G.:																
Asthma	47	106.4	3.	111	.5	.08	.14	0.	5.5	0.	.06	0.	.10	1.	.14	.24
				146	.2 (.7)	.04	.12	.7	6.5 (4.2)	2.	.07	− .4	.07	3.3	.12	.14
A. R.:																
Gonococcal arthritis	34	106.4	3.	104	.8	.08	.22	0.	6.	0.	.065	.2	.08	1.2	.14	.29
				162	.M	M	.2M	0.	8.5 (4.5)	0.	.045	− .2	.06 (.11)	2 (.6)	M	.2M

LEAD II.

	Age.	Highest temp., °F.	Hrs. of 104 or over.	Rate per minute.	P amplitude.	P duration.	P-R.	Q.	R.	S.	Q-R-S interval.	RT level displacement.	RT duration.	T amplitude.	T duration.	TQ interval.
H. L.:																
Gonococcal arthritis	38	106.1[R]	5.5	76	1.6	1.	.15	.4	10.	0.	.08	.3	.14	2.	.14	.40
				109	1.	.08	12	.9 (.7)	7 (12)	0.	.06	.0	.06	3.5	.22	.18
B. M.:																
Gonococcal arthritis	36	105.8[M]	3.5	92	2.	.08	16	.0	8.5	1.25	.08	.0	.08	2.	.15	.34
				133	3.	.09	12	.0	17.	0.	.07	−.25	.04	$-\frac{1}{4}$ +$\frac{1}{2}$ b	.26	.12
E. H.:																
Multiple sclerosis	44	104.	?	97	1.4	.09	12	.0	10.	0.	.08	−.3	.12	−1.	.11	.28
				116	.9	.08	10	.0	3.	.7	.05	−.8	.10	−.4	.08	.22
M. L.:																
Gonococcal arthritis	20	106.1[R]	5.	67	.8	.08	16	.0	11	0.	.06	.2	.16	2.1	.16	.60
				146	1.5 (.6)	.08	16	.5	7.5	.3	.04	.0	.07	3.	.20	.15
M. J.:																
Non-specific infectious arthritis	42	106.8	5.	72	.7	.08	20	.0	4.2	2.2	.08	.4	.09	2.7	.16	.48
				162	1.8 (.3)	.10 (.06)	18	.5	2.4	.7	.07	−.2	.05	1.4	.11	.16
H. H.:																
Non-specific infectious arthritis	20	105.9[M]	5.	81	1.	.07	14	.0	5.5	3.	.08	.0	.06	3.	.15	.24
		106.1[R]	...	120	1.4	.10	13	.0	6. (4.5)	5 (2.5)	.08	.0	.05	2.	.14 (.16)	.22
E. G.:																
Gonococcal arthritis	29	105.5[R]	3.5	84	.2	.08	13	.0	12.	.8	.08	−.3	.10	.8	.16	.36
				130	1.2	.08	16	.0	9.	0.	.05	.0	.12	1.9 (−.4 +.2 b)	.14 (.20)	.19
*E. H.:																
Gonococcal salpingitis	25	105.7[M]	4.	102	1.2	.08	15	.3	15.5	3.	.07	.0	.10	2.4	.14	.28
				150	.6	.06	12	.0	8.	.7	.05	−.4	.09 (1.2)	0.	.18 (.12)	.13
*J. G.:																
Asthma	47	106.4	3.	113	2.1	.08	16	.0	7.	0.	.08	.0	.05	2.4	.20	.20
				146	1.7 (2.6)	.08	15	.7	3.5	3.	.06	−.5	.11	6.	.12	.14
A. R.																
Gonococcal arthritis	34	106.4	3.	104	1.6	.09	23.	.0	13.	0.	.08	.2	.08	1.4	.16	.26
				158	M	M	20M	.0	7.	0.	.045	−.4	.11	2.2	15M	21M

Lead III.

	Age.	Highest temp., °F.	Hrs. of 104 or over.	Rate per minute.	P amplitude.	P duration.	P-R.	Q.	R.	S.	Q-R-S interval.	RT level displacement.	RT duration.	T amplitude.	T duration.	TQ interval.
H. L.:																
Gonococcal arthritis	38	106.1	5.5	81	.7	.07	.15	0	3	0	.08	.3	.16	.5	.10	.40
				111	1.2 (.6)	.09	.13	0	5.5	0	.09	0	.04	2.5 (−.3 + .8 b)	.22	.13
B. M.:																
Gonococcal arthritis	36	105.8	3.5	94	.5	.07	.16	.1	−3.5	1	.09	0	.10	−.1	.08	.36
				133	.2	.08	.12	−.4	−.8	.5	.08	.25	.04	−.4	.16	.18
E. H.:																
Multiple sclerosis	44	104	?	97	.7	.07	.12	0	.2	−.7	.07	0	.18	−.5	.08	.26
				120	.5 (+.3 − .6 b)	.06	.10	1	−.3	−2.5	.06 (.08)	−.2	.10	.4	.06 (.10)	.20
M. L.:																
Gonococcal arthritis	20	106.1	5	71	.3	.04	.16	.3	.5	0	.055	0	.18	.8	.14	.68
				143	.7	.08	.15	1.4	.7	0	.05 (.06)	0	.07	1.6 (−.8)	.10 (.20)	.15
M. J.:																
Non-specific infectious arthritis	42	106.8	5	73	−.1	.07	.18	0	1.6	−.6	.08	0	.18	−.7	.10	.46
				167	1	.10	.12	.7	−3.5	1	.06	0	0	1.	.16 (.08)	.16
H. H.:																
Non-specific infectious arthritis	20	105.9[M]	5	102	+.3 − .5 b	.08	.14	2.2	4.5	0	.07	0	.07	.6	.12	.32
		106.1[R]		125	.6	.07	.13 (.16)	3.5	7.5 (2.)	0	.07	0	.12	.8 (.3)	.08 (.16)	.21
E. G.:																
Gonococcal arthritis	29	105.5	3.5	82	−1.4	.08	.16	0	.9	0	.07	0	.16	−.7	.12	.37
				133	.8	.06	.12	.6	.5	0	.06	.3	.08	.7	.08 (.16)	.14
*E. H.																
Gonococcal salpingitis	25	105.7	4	102	.8	.07	.12	0	1.4	2	.08	0	.10	−.3	.10	.30
				146	.4 (1.)	.08	.10	.6	−.2	4 (−.3)	.065	−.3	.08 (.12)	−1.2 (+.4)	.08 (.16)	.11
*J. G.:																
Asthma	47	106.4	3	111	1.6	.08	.16	0	.2	0	.07	0	Flat	.5	Flat	Flat
				146	2.2 (1.1)	.09	.14	2.	2.6 (−1.4)	1.	.08 (.05)	.2	.14 (.09)	2.	16. (10)	16
A. R.:																
Gonococcal arthritis	34	106.4	3.	109	.8	.10	.23	0	.7	0	.08	0	.04	−.4	.12	.36
				158	2.M	M	21M	0	1.5	0	.04	0	.16	.8	10M	.22M

In 1 instance a 2 mm. T wave was flattened to the isoelectric level and in another a 2 mm. erect T wave was made biphasic.

In Lead III, in 3 instances an inverted T wave became erect.

Both increases and decreases occurred in each of 3 cases in Lead I, 2 cases in Lead II, and 4 in Lead III.

The duration of the T wave was only slightly more often diminished than increased (10 to 8). In Leads I, II and III, there were decreases in 5, 4 and 1 case respectively, and increases in 3, 3 and 2 cases. In the remainder, both increases and decreases were present in each case.

The T–Q periods from the end of the T wave to the beginning of the Q–R–S complex, the period of diastole, naturally diminished with the increase in rate. The relative change here, however, was greater than the relative change of the whole cycle length. The greatest diastolic reduction was from .68 to .15 second, over 78%, whereas the cycle length (R–R) was reduced only 50%, from .84 to .42 second for the same cycle.

From the above analysis and from references to the tables it is readily seen that fever, particularly the higher fevers, occasionally affected the electrocardiogram significantly. Some normal wave amplitudes and intervals, have become abnormal under its influence. Several abnormal values too were so altered as to come within the normal range. Expecially striking was this for the R and T wave amplitudes, the P–R interval and in 1 case the Q_3 depth. The appended table indicates in some detail the changes that occurred. Because of the small number of cases it is incomplete, but at present does give some idea of changes that may be attributed to fever.

Many of the electrocardiographic changes are probably due to the increase in rate. We have seen most of these P, Q–R–S and T wave changes produced by simple sinus tachycardia caused by exercise in a normal afebrile adult. However, we do not believe that the rate increase explains all. The group of chemical and physiologic changes which take place in fever, undoubtedly contribute to and modify the electrocardiographic effects of increased rate. These are especially the alterations in blood and tissue pH, carbon dioxid and lactic acid content,[7,8,9] etc., and in addition the changes in metabolism, blood pressure, blood flow and cardiac output.[1,7,8,9,10]

The electrocardiographic variations pretty much paralleled the temperature and rate changes. Starting with the beginning of the fever, they gradually reached their maximum at about the height of the temperature and receded with the temperature, frequently with some lag.

In most cases, there was a return of the electrocardiogram to the pretreatment appearance either immediately upon the cessation of the fever or shortly after. Alterations of interval were restored more promptly than the alterations of amplitude. No change was permanent. From these electrocardiographic changes, it cannot be inferred that any cardiac damage had been produced by the hyperpyrexia.

Summary and Conclusion. Observations were made on changes in electrocardiograms produced by fever of between 104 to 106.5° F., of 3 to 5 hours' duration, induced by physical means.

Changes in rate were described.

The alterations of electrocardiographic waves were not uniform. P and T waves were almost as frequently increased in size, as decreased. The R wave, however, most often became smaller and the P–R and Q–R–S intervals in most instances were shortened.

The RT level was usually depressed, never elevated.

Of special significance was the transformation of several normal

amplitudes or intervals to abnormal ones, as well as the reverse. This involved particularly the R and T amplitudes. Worthy of mention is the development of a prominent Q_3 in one instance.

The mechanism of electrocardiographic changes is probably through reflexes, tachycardia, local cardiac and general chemical and physiologic alterations.

None of the electrocardiographic changes were permanent. No inference could be made that the fever produced any harmful effects upon the heart.

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STRENGTH DURATION CURVES OF THE OVEREXCITABLE AND UNDEREXCITABLE NERVE MUSCLE APPARATUS AND SOME CONSEQUENCES BEARING ON THE CLINICAL APPLICATION OF CHRONAXIMETRY.*†

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Lapicque has proven experimentally that the strength duration curve of different tissues—except for very short times—was approximately an hyperbola. This conception was completely corroborated by Sakamoto (1933) stimulating single motor nerve fibers.

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Corresponding to the definition of the hyperbola, two determinations —representing rheobase and chronaxie—should, therefore, determine the actual strength duration curve and simultaneously the irritability of the examined tissue. It is the teaching of the French school that even one of them, the chronaxie, should determine exactly enough—at least for clinical purposes—the irritability of a given tissue. The simplicity of this one figure as a result of the electrical stimulation is the more appealing, as Lapicque had assumed a fixed relation of 4 to 1 between chronaxie and his time constant θ.

Lapicque's experience, however, was confined mostly to the normal nerve muscle apparatus. Whether chronaxie alone is a suitable index of irritability under pathologic conditions also, is still open to discussion.

The practical application of chronaxie in clinical medicine depends, therefore, upon the following questions:

1. *a.* Whether the strength duration curve of the overexcitable and underexcitable nerve muscle apparatus is an hyperbola as well as that of the normal one; and if that is true:

b. In what way the hyperbolæ of overexcitable and underexcitable individuals differ from the normal and from another.

2. What symbol can best characterize the shape of these curves.

Eight hundred and twenty-five lead workers subjected to different degrees of exposure were chronaximetrically examined at the superior optimal point of the extensor digitorum communis percutaneously by means of a condensor apparatus with about 11,000 ohms resistance and with help of a constant source of current read off to 1 v.

§ 1. The *strength duration curve of normal, of definite overexcitable and definite underexcitable* individuals was established on about 6 points. Figure 1 gives a number of such curves; Figure 2 shows representatives of each of these 3 categories in a larger scale.

a. Plotting quantity against time, it was found that the Weiss-Hoorweg line in all three curves of Figure 2 was a straight line—except for very short times. This observation emphasizes the probability that the *curves are in fact hyperbolæ.*

To verify the result, according to Hoorweg's formulæ of the strength duration curve, the constants a and b were calculated from two determinations of voltage and time (1 and 3 of the following example). The resulting figures were put into a third value next to or between the two first (middle value of the example) and the voltage was calculated. The calculated voltage and the observed voltage differed from 3 to 7.5%.

Normal.		*Overexcitable.*		*Underexcitable.*	
200V—0.16σ		135V—0.8σ		200V—0.16σ	
190V—0.48σ	205V = 7.9%	110V—2σ	116.5V = 5.5%	175V—1.36σ	169.6V = 3%
160V—1.4σ		100V—7σ		150V—2σ	
a = 72		a = 47		a = 8.6	
b = 155		b = 93		b = 145.7	

b. Comparing the shape of the curves in Figures 1 and 2, we observe that they are entirely different in their curvature. The curvature is smallest in overexcitability and greatest in under-

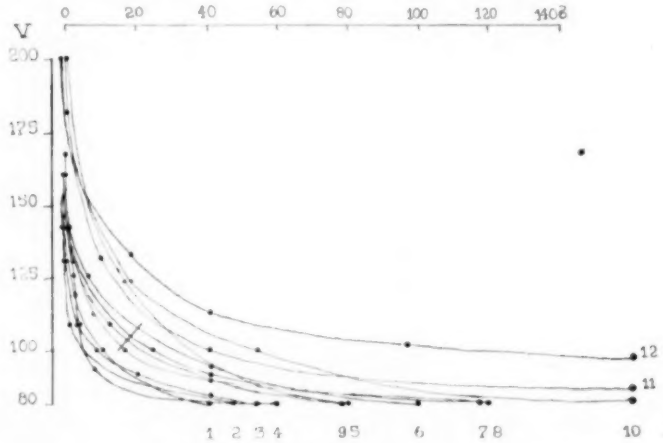

FIG. 1.—A number of strength-duration curves from overexcitable, normal and underexcitable individuals. The line uniting the vertex points is drawn only in the range of the normal.

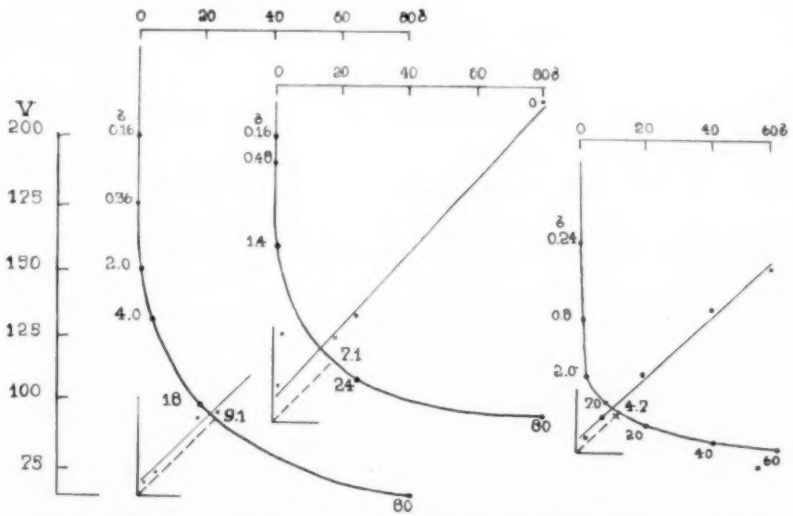

FIG. 2.—Three strength-duration curves, from the left to the right characteristic of an underexcitable, a normal and an overexcitable subject. The right angles signify the position of the respective zero point of the coördinate axes. The dotted line bisecting this angle intersects the curve in its vertex. The vertex characterizes the shape of the curve (hyperbola). Its index is equal to the square root of the product of rheobase and chronaxie (vc.). The full straight line connecting the various points is the Weiss-Hoorweg line.

excitability, and lies between the two values in normal individuals. This means that *the curvature formed by the two branches of the strength duration curve characterizes the degree of irritability.*

§ 2. If this is true, the best symbol of the strength duration curve would be an index giving the clearest reading of the curvature. The position of the *vertex of the hyperbola, i. e.*, the vertex coördinates, would best serve this purpose.

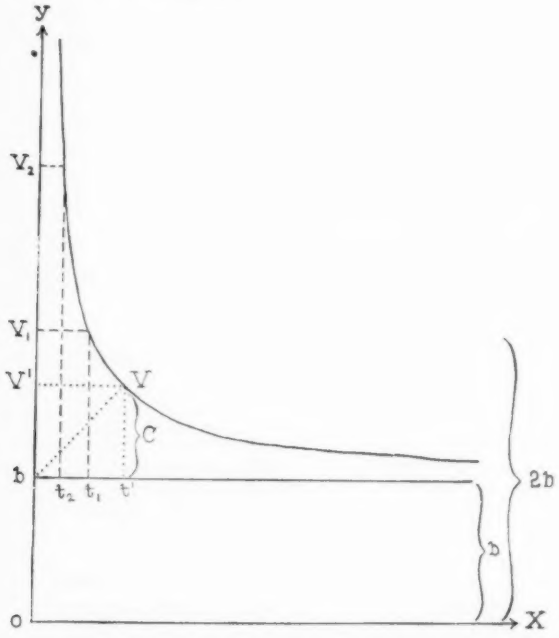

FIG. 3.—Diagram of a hyperbola within a rectangular coördinate system: x = time axis, y = volt axis, b = rheobase. The corresponding chronaxie determined with 2b (V_1 Volt) is equal to t_1. t_2 designates the time with a voltage somewhat higher than the doubled rheobase (V_2). V = vertex of the hyperbola, V′ and t′ the corresponding voltage and time. VV′ = Vt′ = C.

The straight line bisecting the right angle of the coördinate system, formed by the vertical volt axis and the horizontal time axis at the level of the rheobase *b*, intersects the hyperbola in its vertex (Fig. 3). The position of the vertex, according to the definition of the hyperbola, can be calculated as the square root of the product of rheobase by chronaxie, *i. e.*, of half of the quantity. The length of this vertex coördinate was measured in determined and outlined strength duration curves and compared with the results of hundreds of calculations in normal and pathologic individuals as to our test muscle (extensor digit. comm.). This muscle has a normal rheobase of 90 to 45 volts with a corresponding chronaxie of from 0.4 to 0.8σ. The statistical norm of the vertex co-

ordinate under these conditions was between 6 and 9 units of measurement. Figures below 6 indicate a more rectangular curve—as characteristic of overexcitability—while figures above 9 give a more obtuse angle—as characteristic of underexcitability.

The given formula (I) $C = \sqrt{rh \times chr}$, in which C designates the vertex coördinate, rh the rheobase and chr the chronaxie, makes it obvious that the rheobase cannot be a negligible factor, as even with identical chronaxie the shape of the hyperbola varies widely subject to the rheobase. This is not so important in normal cases, as normally the rheobase is relatively constant with the same resistance and the same muscle. But with a change of temperature and blood flow or under the effect of different mineral salts and drugs the rheobase may be indispensable for final decision, especially when the chronaxie is verging upon overexcitability or underexcitability.

In *physiological experiments* it is certainly the most suitable procedure to plot quantity against time, to control the straightness of the Weiss-Hoorweg line and to compare it in a diagram with an average standard line. For *routine neurological examinations*, however, this method is somewhat complicated. We found a simpler method in deriving the vertex coördinate of the correspondent hyperbola directly from the determinations.

According to Figure 3: $C = \sqrt{V_1 t_1 - b t_1} = \sqrt{V_2 t_2 - b t_2}$. If t_1 is the chronaxie, V_1 its double rheobase, *i. e.*, 2b:

(I) $C = \sqrt{(2b - b)t_1} = \sqrt{bt_1} = \sqrt{\text{rheobase x chronaxie}}$. (I) First determination.

(II) $C = \sqrt{(V_2 - b)t_2}$ Valid for a second pair of determinations, *e. g.*, 20V above the doubled rheobase.

(III) $C = \sqrt{\dfrac{(V_2 - V_1)t_2 t_1}{t_1 - t_2}}$ Determines C in a somewhat different way.

Substituting the observed values into the formulæ I to III the values of C usually vary in some degree. The mean value of the three readings—to be called *vertex characteristic*, vc.—seems to be a good symbol of the hyperbola representing the strength-duration curve.

We preferred this form of presentation, going down to the coördinate C for its greater visuality and for the direct comparability of the obtained results with those measured in determined and outlined strength-duration curves. The square root of the product of voltage and time is so easily read off from a table that we applied the square root not only in these theoretical deductions but also in our practical examinations (Lane and Lewy, 1935). However, there is no objection in resigning to draw the root and in using the constant C^2 instead of C. Under these conditions the norm in our case is from 36 to 81 instead of from 6 to 9.

§ 3. In order to prove this statement it will be shown that:

(*a*) The vertex of the strength-duration curve, calculated according to the three given formulæ from two pairs of measurements coincides in first approximation with the vertex of the observed curve, and

(*b*) The ordinate of the hyperbola constructed at the "calculated" vertex (as above) coincides approximately with a third "observed" point of the curve which is not used in the calculation.

a. We designate the vertex characteristic vc. as "calculated" when it represents the mean of the 3 results determined with help of formula I to III. We designate it as "observed" when it represents the measured vertex coördinate of the determined strength duration curve outlined on millimeter or inch paper.

			Calculated vc.	Observed.
1.	100V—0.28σ . . . I. 5.2	III. 3.8		
	175 —0.56σ . . . II. 6.4	vc. 5.1	5.1	5.0
2.	65V—0.32σ . . . I. 4.5	III. 3.6		
	150 —0.16σ . . . II. 3.7	vc. 3.9	3.9	3.5
3.	70V—0.2σ . . . I. 3.8	III. 2.4		
	120 —0.6σ . . . II. 5.4	vc. 3.9	3.9	4.1
4.	80V—0.24σ . . . I. 4.4	III. 3.2		
	130 —0.8σ . . . II. 6.3	vc. 4.6	4.6	4.7
5.	95V—0.48σ . . . I. 6.7	III. 4.7		
	160 —1.4σ . . . II. 9.5	vc. 7.0	7.0	7.5
6.	80V—0.68σ . . . I. 7.4	III. 6.6		
	200 —0.36σ . . . II. 6.6	vc. 6.9	6.9	7.0
7.	90V—0.8σ . . . I. 8.5	III. 7.5		
	200 —0.7σ . . . II. 8.8	vc. 8.3	8.3	8.4
8.	65V—0.6σ . . . I. 6.2	III. 7.7		
	150 —0.5σ . . . II. 6.5	vc. 6.8	6.8	6.2
9.	65V—4.0σ	III. 8.9	8.9	9.8
10.	65V—4.0σ . . . I. 16.0	III. 6.3		
	170 —0.8σ . . II. 8.6	vc. 10.3	10.3	10.7
11.	80V—2.8σ . . . I. 14.4	III. 6.7		
	200 —0.8σ . . II. 9.8	vc. 10.3	10.3	9.7
12.	70V—4.0σ . . . I. 16.8	III. 10.3		
	180 —0.8σ . . . II. 8.5	vc. 11.9	11.9	12.2

Although the decimals of the observed values are merely estimated and consequently inaccurate, *the coincidence of calculated and observed vertex coördinates is very satisfactory.*

b. For reasons which will be discussed in § 6 anode strength duration curves were observed and were constructed as hyperbolæ at the calculated vertex, according to the 3 given formulæ. Furthermore, in all of these curves the time was determined at the level of the doubled cathode rheobase. This third "observed"

time value, not used in the calculation, was compared with the time of the constructed curve at the same level.

Calculated time.	Observed time.
2.2σ	1.4σ
0.8σ	1.2σ
6.8σ	6.8σ
3.5σ	4.0σ

As the first column represents points of a mathematical curve, and the second represents values of percutaneous measurement, and therefore relatively inexact, the correspondence seems quite satisfactory.

We may accordingly conclude that:

1. *Strength duration curves of the overexcitable and underexcitable nerve muscle apparatus are hyperbolæ, differing in the degree of their curvature.*

2. *By means of two independent measurements of the excitation time—one of which may be the chronaxie—and by three simple calculations we can determine the "vertex characteristic" (vc.). This symbol defines with sufficient exactitude the shape of the hyperbola upon which the chronaxie is situated.*

From these theoretical deductions follow practical consequences which seem to be of importance in the application of chronaximetry to clinical medicine.

§ 4. Every experienced examiner knows how difficult it often is to determine even in normal individuals in percutaneous examination the optimal point. Under pathologic conditions it may remain still more questionable whether the point stimulated at the skin is really the most irritable. In consequence of this experience even so skillful an investigator as Bourguignon emphatically reiterates that one should not rely on the result of one single chronaximetric examination unless it be verified by a second and third investigation.

These experiences made it desirable to evolve a *routine method* permitting it to be established *whether or not the stimulated point is really the optimal one.* We designate as the "optimal" point the most irritable one, or more exactly, such a point on the skin by stimulation of which the virtual cathode within the nerve gets its greatest density. If this point is stimulated with a higher voltage, the time required for excitation decreases *pari passu*, while the product of the two, after subtraction of the rheobase, remains equal. This is not so if any other point at the skin is stimulated. It has been our experience that if such a non-optimal point is stimulated with a higher voltage, the corresponding time does not seem to decrease in reciprocal ratio; consequently the product of voltage by time is not unvariably the same. In other words, on

stimulating the optimal point on the skin, the strength duration curve is a hyperbola; while on stimulating any other point this does not seem to be the case.

This result of a great number of investigations in pathologic conditions coincides with the findings of Büssow in normal individuals. Büssow showed that stimulating a skin point in the distance of $\frac{1}{2}$ inch from the real optimal point the strength duration curve of a normal muscle may become discontinuous.

As it is impossible in routine medical examinations to determine each time the whole strength duration curve, it is certainly advisable to determine, instead of one, at least two points of the curve, and to prove that they are part of the same hyperbola.

§ 5. However, *in the first stages of a nerve lesion*—though depending on its character—and in the last stages of regeneration, it is usually *impossible to obtain a satisfactory approximation* of the three values of vc. This implies that not all points of this strength duration curve were situated upon one and the same hyperbola. In fact, Adrian has shown on the degenerated facial nerve that *such curves, as a rule, are discontinuous.*

This fact, of course, is not rendered visible if the chronaxie alone is measured, nor is it apparent in the vertex characteristic calculated from chronaxie and rheobase only. But it may be suspected, if one cannot get a close approximation of the three vertex values, especially when the values of formula III spread over a wide range.

(I)	V_1 (rheobase)	80V, t_1 (chronaxie)	3.6σ vc. 16.9
(II)	V_2	200V, t_2	1.6σ vc. 13.8
(III)			vc. 10.9

Under these conditions we are able to calculate the rheobase of the assumed second hyperbola and its vertex from V_1, t_1 and t_2 by formula IV.

$$\text{(IV)}\quad b = \frac{V_2 t_2}{t_1 + t_2} = \frac{200 \times 1.6}{3.6 + 1.6} = 61.5\text{V}$$

Let us suppose, according to this calculation, that the two determined points are part of two hyperbolæ, the rheobases of which are 80 and 60 V respectively, then we can record it as in Figure 4. The full line in Figure 4 shows the discontinuous curve, as the combination of both the dotted and the lined hyperbola. Assuming the breaking point of the curve at 160 V was the rheobase of the superior (full) curve the chronaxie of this hyperbola was 0.88σ, *i. e.*, about normal. This corresponds to Adrian's curves. He found the chronaxie of the steep part of the curve during the process of degeneration practically unchanged, while the chronaxie of the flat curve increased gradually. Not until the degeneration was complete was a uniform smooth hyperbola again found, now with an obtuse curvature.

§ 6. Finally, we followed up the *anode excitation time* in connection with Pflüger's law. Some of the anode strength-duration curves were determined, others were calculated and constructed on the basis of their vertex characteristic. Figure 5 shows that in the majority of our cases the threshold for the cathode was lower than that for the anode. We did not observe in our cases a reversal of the galvanic excitability. The difference between the cathode and anode threshold was greater in pathologic than in normal muscles.

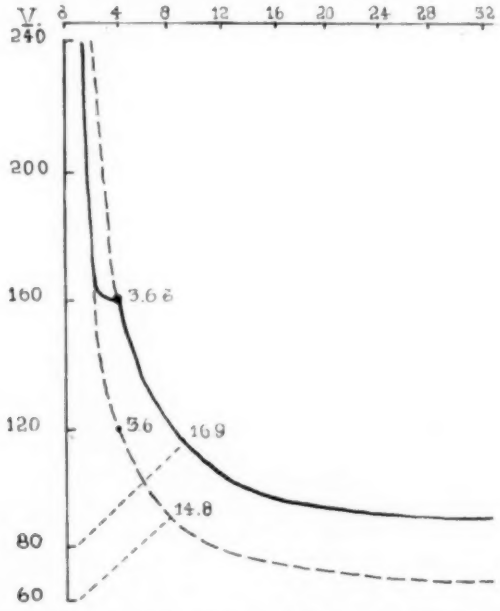

FIG. 4.—Diagram illustrating the constituents of a discontinuous strength-duration curve. It results in the combination of two (constructed) hyperbolæ. The chronaxie of the superior curve is normal with 0.8σ, that of the inferior is underexcitable with 3.6σ.

The most interesting fact, however, seemed to be *the crossing of the cathode and the anode curve upon the vertical axis as a first step towards the inversion of the excitation law.* This means that at the level of the doubled cathodic rheobase the anode excitation time became shorter than that of the cathode excitation time. In other words, *the excitation rule and its inversion applies* not only and not primarily to the galvanic threshold but *also and even earlier to the excitation time* (Fig. 5, curves 4*a* and 4*b*).

Discussion and Conclusions. In looking through the literature on clinical chronaximetry we see that almost constantly the rheobase values were omitted in the results, although they had to be determined to get the chronaxie values. Such a procedure may be per-

missible under certain conditions but not so as a rule. Local anesthetics, for instance, will, according to their concentration, increase the rheobase and decrease the chronaxie with the effect that their product, the minimal electrical quantity required for stimulation, remains about the same in cocain and novocain narcosis, but is considerably increased in pantocain and percain narcosis (Laubender and Raufenbarth). Exact consideration of the rheobase is also

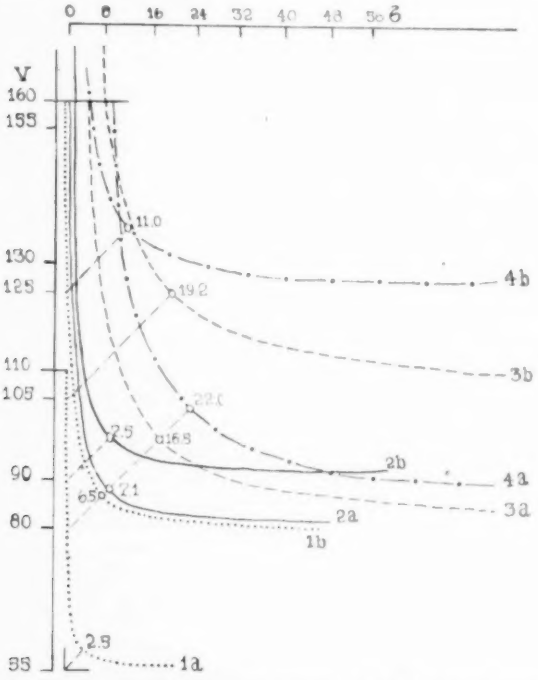

FIG. 5.—Four pairs of strength-duration curves. Each pair represents the cathode (*a*) and the anode curve (*b*) of one individual; 1*a* and *b* of an overexcitable, 2*a* and *b* of a normal, 3*a* and *b*, 4*a* and *b* of two underexcitable subjects. With the exception of 4*a* and *b* rheobase and chronaxie is shorter at the cathode than at the anode. With progressing underexcitability, however, the anode chronaxie becomes shorter than the cathodic one (4*a* and *b*), even before the anodic threshold grows smaller than the galvanic threshold (galvanic overexcitability). First stage of inversion of Pflüger's law.

required in order to understand the changes of nerve irritability under physiologic conditions such as during hyperventilation or anoxemia in great altitudes. *Neither rheobase alone nor chronaxie alone give the right impression of irritability.* The rheobase, however, gets its significance only through chronaxie. If that is so it is very important that *both parameters of irritability be included in the given result;* and that the rheobase should not be omitted. On the other hand, the simultaneous comparison of two rheobase and two chron-

axie values complicate the method for practical use. The length of one of the equal coördinates of the vertex of the hyperbola, representing the strength duration curve, is likewise given by one figure only. But since this one figure equals the square root of rheobase and chronaxie, it helps, in fact, to get rid of the rheobase. That is the reason this figure is superior to chronaxie alone. It, furthermore, conveys a clear idea of the shape of the hyperbola in representing a definite strength duration curve.

There are, no doubt, many cases in which a single chronaximetric examination and the statement of chronaxie alone give results sufficiently unequivocal to render any further test superflous. We class under this heading the majority of normal cases and all distinctly abnormal, more particularly underexcitable, subjects. Such clear cases, however, are found less frequently than may be supposed. Applying chronaximetry to persons not ill in the proper sense but exposed to noxious agents, as in industry, a greater part of the subjects examined was found to be on the borderline between normal and abnormal (Lane and Lewy, 1935). This is where the new index proved very helpful.

The same question has to be considered concerning the *optimal stimulation point* of a muscle upon the skin. This point is seemingly very easily found from one of the textbook diagrams. But in reality the situation of this point varies even in the normal from man to man. Under pathologic conditions the point may sometimes be hardly greater than a pinhead. The superior and inferior optimal point showing entirely different normal values, may be distant only $\frac{1}{4}$ inch from one another. Finally, no reliable chronaxie may be obtainable at the point of the lowest galvanic threshold. If, however, to overcome these difficulties greater capacities and lower voltage is applied, the skin is charged in increasing degree and the rheobase varies from one experiment to the next. To avoid this a much higher resistance (of ca. 100,000 ohms) in series to the skin would be required, with a corresponding higher voltage. This again is too dangerous in man and involves other difficulties (sparks, etc.). Accordingly, sufficient time must be allowed to elapse before the determination is repeated. But if the same point is stimulated several times in succession, especially with longer duration, the time values begin to flicker. Even with considerable experience in chronaximetric measuring, it may in pathologic cases take a quarter of an hour or longer to find the correct chronaxie of a single muscle point.

These observations lead to the setting up of the postulate that the correct position of the stimulation point should be objectively demonstrable. By determining besides rheobase and chronaxie a second time value with a strength of current about 20 V above the doubled rheobase, and by a simple multiplication, it seems to be possible to state with an accuracy sufficient for percutaneous clinical

examinations whether or not the optimal skin-muscle point is stimulated or whether the curve is discontinuous. In this case the rheobase of the second hyperbola can be easily extrapolated. Such a procedure proved to be more important as our examinations, corresponding to those of Adrian, showed that the discontinuous strength duration curve is neither a rare occurrence nor always the sign of an error in technique. The discontinuous curve rather represents a regular, though temporary stage during degeneration and regeneration.

Finally, our observations on Pflüger's law indicate a facilitation of the routine work in underexcitable cases. The direction of current has to be reversed at any rate during each examination, in order to counteract the skin polarization. What remains to be done in the quoted cases is to observe at this time whether the same condenser, the discharge of which produces the first twitch at the cathode is effective at the anode as well. If so we are faced with the first indication of a qualitative alteration of Pflüger's law.

Summary. Although it is generally accepted that the strength-duration curves of the normal nerve muscle apparatus are approximately hyperbolæ this has not yet been proven under pathologic conditions, *i. e.*, in overexcitability and underexcitability.

1. By means of chronaximetrical examinations of 825 lead workers subjected to different degrees of exposure it could be shown that the strength-duration curves of the overexcitable and underexcitable nerve-muscle apparatus equal approximately a hyperbola.

2. The hyperbolæ of normal, of overexcitable and underexcitable individuals differ in the degree of their curvature. The legs of the hyperbola of an overexcitable muscle form a more acute curvature, those of an underexcitable a more obtuse curvature. Normal curves lie between the two extremes.

3. The most suitable symbol of characterizing an actual strength-duration curve and indicating simultaneously its shape is the vertex of the hyperbola. The coördinate of the vertex—which may be called "vertex characteristic" (vc.)—equals the square root of the product of rheobase by chronaxie or in other words of half of the quantity. By this method one single and easily comparable figure is obtained. This single figure unmistakably characterizes the actual strength-duration curve.

4. Three simple formulæ are given to calculate the vertex characteristic by help of two independent pairs of measurements, carried out at one and the same muscle point. The approximate coincidence of the three values seemed to confirm that it was really the optimal point that was stimulated.

5. In the first stage of nerve degeneration and in the last stages of regeneration not all points of the strength duration are situated upon the same hyperbola. The curve becomes discontinuous, indicating that it consists of two distinct hyperbolæ. Under these con-

ditions the rheobase of the second hyperbola can be calculated by a simple formula from the two determinations.

6. The inversion of Pflüger's law applies to the excitation time as well. Even before the galvanic threshold with the anode sinks below the threshold with the cathode, the excitation time with the anode becomes shorter than that with the cathode.

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IS THE USE OF INSULIN INDICATED IN THE ELDERLY DIABETIC WITH CORONARY SCLEROSIS?

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Warning notes have appeared in the literature against the use of insulin in the diabetic who has manifestations of vascular degenerative disease because of the danger of precipitating vascular spasms or thromboses during hypoglycemic attacks.

Vascular crises are recognized to occur most commonly in arteries that have undergone sclerotic degeneration as a result of essential hypertension or progressive involution with aging. Reports in the literature[1,2,3] indicate that these sclerotic lesions are a more frequent phenomenon in the diabetic than the non-diabetic and in the poorly treated diabetic than in the well-controlled diabetic.

This paper is concerned with a critical analysis of the use of

insulin and an expression of opinion as to whether there is adequate justification for the feeling that insulin is contraindicated in the treatment of the elderly diabetic.

Before discussing this subject, it is well to review some of the physiologic and pharmacologic properties of insulin. In the pancreatectomized animal, insulin produces a disappearance of sugar from the blood with an attendant rise in the respiratory quotient, indicating that it is associated with the oxidation of glucose. That insulin also causes the deposition of glycogen in the liver and muscles has been demonstrated by the marked glycogenetic recovery which follows the administration of insulin in animals whose liver glycogen has been depleted by pancreatectomy.[4] Collens and Murlin[5] have suspected a third function of insulin, that of glycogenolysis. They have observed that the injection of insulin into the portal vein produces a transient hyperglycemia which could be explained only on the basis of its coming from liver glycogen. Dudley and Marrian[6] showed that excessive doses of insulin in rats are able to reduce liver glycogen. In view of the observation of Warburg, that the contraction of muscle tissue is associated with the anaërobic oxidation of its muscle glycogen, it would then appear that the function of insulin, in quantitatively regulating the deposition of muscle glycogen would have an extremely important clinical bearing upon the ability of muscle to contract. It is the belief of the authors that the clinical symptoms of muscle weakness and nocturnal claudication which exist as such outstanding symptoms in the diabetic with a severely broken sugar tolerance are the result of the depletion of glycogen from skeletal muscle. The rapid disappearance of these symptoms immediately after the administration of insulin with a liberal amount of carbohydrate helps to confirm our belief that improvement has been attended by the phenomenon of glycogen synthesis in muscle.

The authors who have warned against the use of insulin in the elderly diabetic have based their statements upon definitely observed toxic phenomena produced by administration of this hormone.[7–12] They report various types of disturbances in cardiac function associated with a state of insulin hypoglycemia, such as attacks of paroxysmal fibrillation, angina, and definite electrocardiographic changes, among which are notching of the P waves, prolongation of P–R interval, occasional slurring and prolongation of Q–R–S complex, changes in the deflection of S–T segment and alterations in the character of the T wave, such as flattening, prolongation and diphasic.

Some of these authors[2,7,12] have observed the beneficial effect that glucose has on the anginal attack during the hypoglycemic state. Smith and his co-workers[13] have even commented on the distinct beneficial effect of a high-carbohydrate diet in the treatment of cardiac failure in the non-diabetic. Intravenous injections of

50% glucose have been recommended in the treatment of coronary thrombosis,[14] since it furnishes the heart muscle with extra glucose and has a diuretic effect.

In a paper on poisons, Abel[15] presents an interesting concept of the relationship of poisons to therapeutic agents. To quote from his article: "The harmful effects of a large dose of a drug or poison do not fall off *pari passu* with the diminution in dose. On the contrary, with the diminishing dose there may occur a turn-about in the action of the drug with the appearance of a highly beneficial action, one indeed that is indispensable for the continuance and maintenance of health, as is the case when we pass from the toxic dose of a hormone to its therapeutic dose." Insulin is an excellent example of such a substance, indispensable to life and circulating in our blood below a toxic level, which, when increased in the circulation either by injection or due to hyperfunctioning pancreatic island tumors, results in profound degrees of intoxication violent enough to produce death.

Since insulin is able to deposit glycogen in tissues, we must think of it as a possible therapeutic agent in angina pectoris provided the toxic effect of vascular spasm and depletion of tissue glycogen is strictly avoided. Diabetics suffering from attacks of angina pectoris who showed electrocardiographic evidence of myocardial change as well as those in whom the tracings were normal were selected for this study. All types of cases, mild and severe diabetics, male and female, with and without evidence of organic heart disease, but all complaining of typical attacks of angina pectoris, were given a high-carbohydrate diet with sufficient insulin to relieve the diabetic picture both clinically and chemically. For purposes of brevity we shall present only a few isolated but typical case histories.

Case Abstracts. CASE 1.—Celia K., aged 60, was admitted with a history of typical diabetic symptoms of 3 months' duration and paroxysmal attacks of severe precordial pressure, dyspnea and palpitation for 1 year which had become aggravated since the development of her diabetes. Physical examination showed early bilateral cataracts, a dry and beefy tongue, auricular fibrillation, blood pressure 186/100, liver large and tender, congestive râles at the lung bases and ankle edema. She excreted 37.5 gm. of sugar in 24 hours and showed 1+ acetone. Her fasting blood sugar was 264 mg.%. She was put to bed, given a diet of C., 200, P., 60, F., 100 (salt-free), with 15 units of insulin, t. i. d., and 15 gm. of available glucose 2 hours p. c., t. i. d. Fluids were restricted to 1000 cc. She was given digitalis (1.5 gr., t. i. d.) and neptal (1.5 cc. intravenously) every other day. In 3 days her fibrillation stopped. Electrocardiogram (Fig. 1), taken at this time, showed evidence of myocardial damage. Two weeks later, she was discharged with her heart compensating and her anginal symptoms gone. Her blood sugar was then 184 mg.% and she showed traces of sugar in her urine. On 2 occasions in the past 18 months she experienced breaks in cardiac compensation precipitated by excessive physical exertion. During these episodes she again fibrillated, but her anginal symptoms were minimal. The interval periods have been entirely

free of anginal attacks. She has been maintained on the above diet and her insulin was reduced to 20 units per day.

Case 2.—George P., aged 64, machinist, 3 months before admission, started to complain of frequent attacks of precordial pain, grip-like in character, and dyspnea brought on by the slightest exertion. He had no diabetic symptoms. He was an obese individual with no positive physical findings except a blood pressure of 180/96. He excreted 2.5% sugar in a casual specimen and his fasting blood sugar was 211 mg.%. His electrocardiogram showed no evidence of myocardial damage (Fig. 2). He was given a diet containing 1200 calories and 258 gm. of available glucose with 35 units of insulin in 2 divided doses. He was protected with postcibal feedings. During the 8 months on this treatment his anginal syndrome has almost entirely disappeared. He does not volunteer any complaints, but on close questioning he states that he is able to elicit a mild precordial discomfort on very marked exertion of an order much out of proportion to that which he previously dared to engage in.

Case 3.—Isidore C., aged 67, was admitted with a history of diabetes of 1 month's known duration. His chief complaint was attacks of precordial pain, with pain also on the right side of his sternum, pressing in character and no radiations. These pains were elicited by walking half a block, and also occurred after meals. The pain was attended by dyspnea, would last 1 to 2 minutes and was relieved by rest. He had no diabetic symptoms. Physical findings disclosed an obese, plethoric, middle-aged man, with heart enlarged, second aortic sound accentuated and blood pressure 170/80. Teleoroentgenogram showed an enlarged hypertensive heart with widening of the aortic arch. Electrocardiogram (Fig. 3) showed evidence of myocardial damage. His urine contained traces of sugar and his blood sugar was 243 mg.%. He was given a diet containing C., 175, P., 51, F., 47, with 10 units of insulin once a day and 15 gm. of carbohydrate 2 hours after his insulin. In the 4 months since he has been on this treatment he has not experienced any anginal pains, either by walking a distance of 7 blocks or after meals.

Case 4.—Reuben M., aged 47, was admitted, April 15, 1932, complaining of attacks of precordial pain radiating to the left arm. He had been diabetic for 11 years. Physical examination disclosed no pathologic findings. Blood pressure, 128/90. Electrocardiogram showed left axis deviation. His urine was free of sugar and his blood sugar 210 mg.%. He was given a diet of C., 150, P., 75, F., 70. After his urine remained sugar-free for 8 months, his tolerance suddenly broke and was followed by an aggravation of his stenocardial syndrome. A reduction in his diet to C., 90, P., 60, F., 70, without insulin controlled his diabetes, but his anginal symptoms persisted. He was then placed on a high-carbohydrate diet, C., 220, P., 60, F., 75, with 10 units of insulin, t. i. d., which was followed by a

Legends for Figs. 1, 2, 3, 4 and 5.

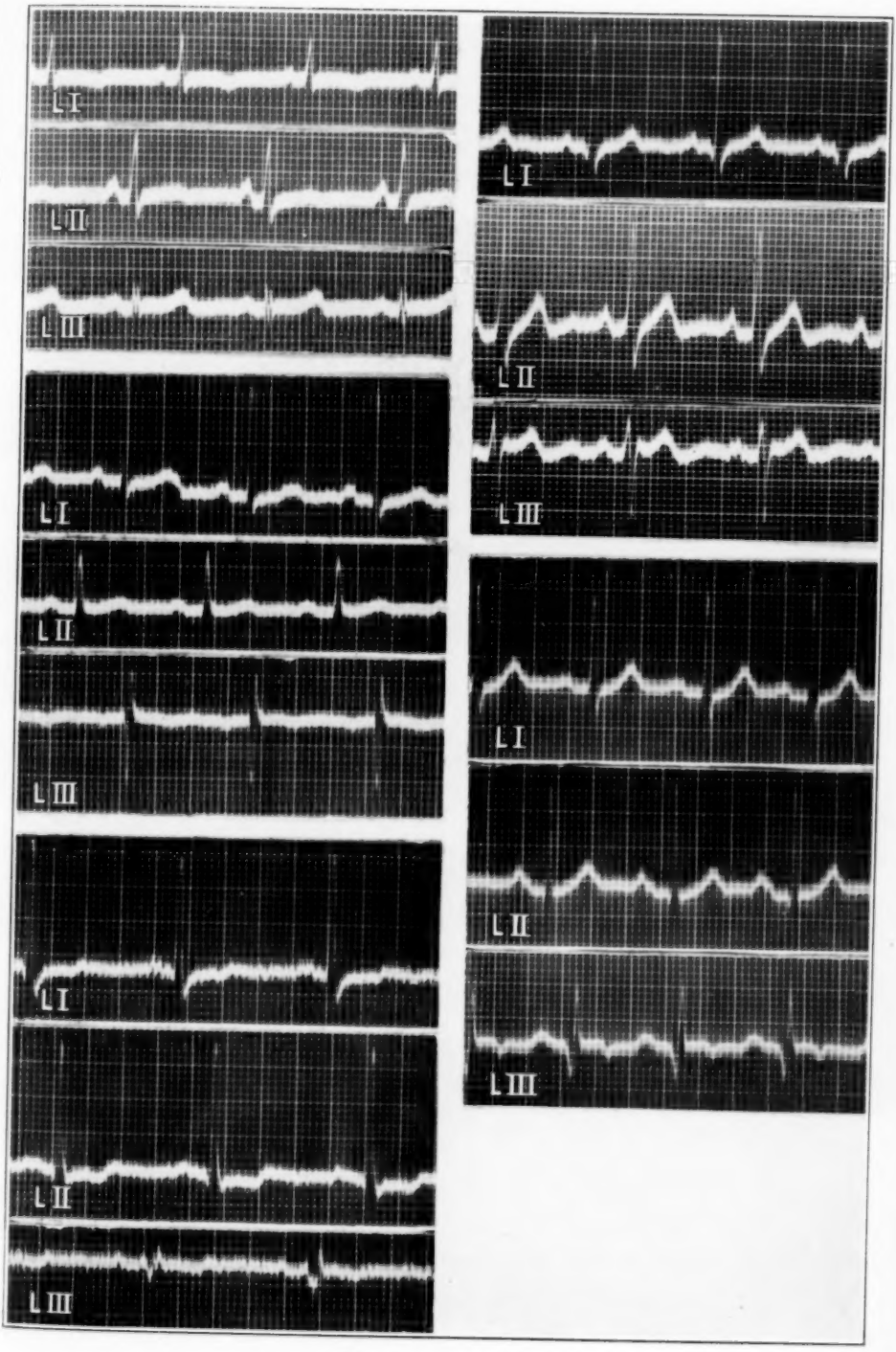
Fig. 1.—Case 1. Lead 1, slurring of upward deflection of *Q R S*; inverted *T*. Lead 2, slurring of upward deflection of *Q R S*; diphasic *T*. Lead 3, slurred *Q R S* complex and low voltage. Diagnosis: Myocardial damage.

Fig. 2.—Case 2. Lead 1, normal. Lead 2, normal. Le ad3, deep *Q*; inverted *P*; inverted *T*. Diagnosis: Normal tracing.

Fig. 3.—Case 3. Lead 1, deep *S* wave; depressed *S T* interval; diphasic *T*. Lead 2, depressed *S T* interval; diphasic *T*. Lead 3, inverted and notched *Q R S*, low voltage; inverted *T*. Diagnosis: Myocardial damage.

Fig. 4.—Case 4. Lead1, normal. Lead 2, deep *S*; tall *T*. Lead 3, inverted *Q R S*. Diagnosis: Left axis deviation. Taken May 12, 1932.

Fig. 5.—Case 5. Normal tracing.



FIGS. 1, 2, 3, 4 AND 5.

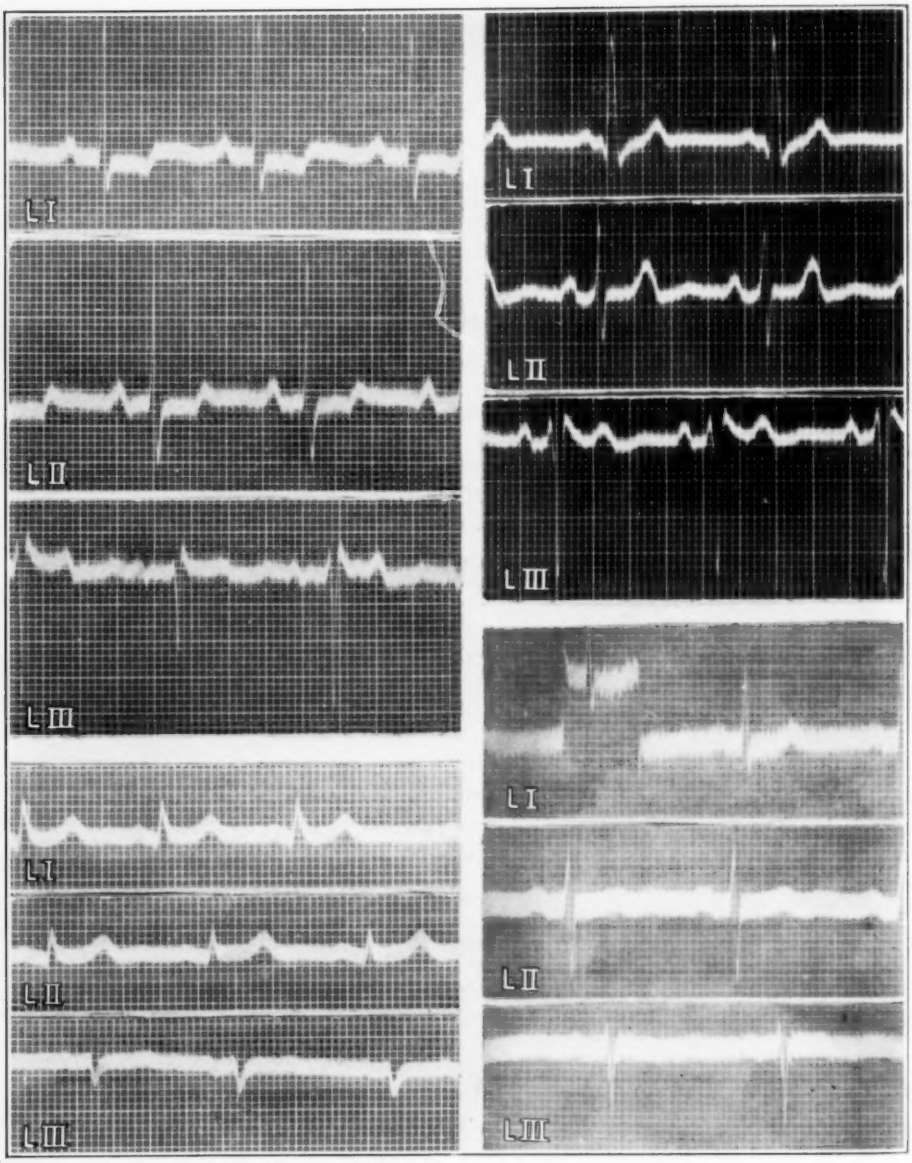


FIG. 6.—Case 6. Lead 1, diphasic *T*; depressed *S T* interval. Lead 2, depressed *S T* interval; deep *S* wave. Lead 3, diphasic *P*; inverted *R*; elevated *R T* interval. Diagnosis: Myocardial damage. Taken November 10, 1932.

FIG. 7.—Case 7. Leads 1, 2 and 3 show slurring of the *Q R S* interval; inversion of *Q R S* interval in Lead 3; low voltage. Diagnosis: Myocardial damage.

FIG. 8.—Case 8. Lead 1, low take-off of *S T*. Lead 2, deep *S* and high *T* wave. Lead 3, high take-off of *S T*. Diagnosis: Myocardial damage.

FIG. 9.—Case 9. Lead 1, slurring of *Q R S*. Lead 2, slurring of *Q R S*; deep *S* wave. Lead 3, slurring of *Q R S*. *Q R S* inverted; *T* inverted. Diagnosis: Myocardial damage; left axis deviation.

prompt and very marked alleviation of his coronary symptoms, a condition which has persisted to date. On October 18, 1934, we wished to determine whether the cessation of insulin would be attended by a return of his symptoms. We thus discontinued his insulin and left him on the same diet. Within a few days there recurred all his previous anginal complaints and at the same time he showed a break in sugar tolerance. The patient was put back on insulin, on November 30, and to date has again been free of anginal symptoms.

Case 5.—Eva P., aged 54, housewife, gave a 4-month history of pruritus vulvi, polyuria, polydipsia, weakness and weight loss and frequent attacks of severe precordial pain for 7 months. Examination disclosed evidence of a hypertensive heart. Electrocardiogram (Fig. 5) showed no evidence of myocardial damage. Blood pressure was 165/90. Because she refused to take insulin she was given a restricted diet consisting of C., 90, P., 40, F., 40, on which she excreted 20 gm. of sugar in 24 hours, and her fasting blood sugar was 220 mg.%. For almost a year her anginal symptoms persisted and were elicited by slight exertion and emotional excitation. When she was finally persuaded to use insulin, she was given a diet containing C., 150, P., 50, F., 50, with 10 units of insulin once a day and an additional 15 gm. of available glucose 2 hours after the insulin. Besides the marked improvement in her diabetic symptoms, her stenocardial syndrome has almost entirely disappeared.

Case 6.—Eva H., aged 62, housewife, had diabetes for 20 years. On her first visit to our clinic, in June, 1931, she was found to be a moderately severe diabetic. On a diet consisting of C., 120, P., 50, F., 65, with 20 units of insulin, b. i. d., she excreted 13.5 gm. of sugar in 24 hours and her fasting blood sugar was 240 mg.%. On September 17, 1931, she began to complain of frequent attacks of precordial pain. She had a hypertensive type of heart, enlarged to the left and a systolic murmur over the precordium. Her blood pressure was 180/100. Her anginal symptoms had progressively increased in frequency and severity, and on November 10, 1932, electrocardiogram showed left axis deviation with myocardial damage (Fig. 6). Her insulin was then increased to 50 units a day in 3 divided doses with a diet containing 190 gm. of available glucose and adequate protection against hypoglycemic attacks. Since the increase in insulin and carbohydrate, there has been a very marked improvement in her anginal symptoms, although she still has occasional but mild episodes.

Case 7.—Fannie L., aged 62, housewife, was admitted to the clinic on July 17, 1934, complaining of the classical symptoms of diabetes—polyuria, polydipsia, polyphagia, weakness and weight loss of 4 months' duration. In addition, she also complained of headaches, vertigo, dyspnea, palpitation and attacks of precordial pain. Examination disclosed an elderly woman, weighing 140 pounds, with manifestations of hypertensive heart. Her blood pressure was 215/90. It was found that she was a mild diabetic, for on a diet of C., 115, P., 65, F., 40, she excreted only traces of sugar and her blood sugar was 148 mg.%. Electrocardiogram showed evidence of myocardial damage and left axis deviation (Fig. 7). In view of her persistent precordial attacks, it was decided to increase the carbohydrate value of her diet by giving her C., 160, P., 60, F., 50, and 10 units of insulin once a day. She has been singularly free of anginal attacks since she started taking insulin.

Case 8.—Sarah L., aged 66, housewife, was first seen, November 5, 1934, complaining of weakness, weight loss, polyuria and polydipsia and a history of having diabetes for 13 years. She also complained of frequent severe anginal pains radiating down the left arm for the past 5 years. Examination revealed evidence of weight loss, a hypertensive heart, sounds of poor quality and a ringing aortic sound. Blood pressure was 190/90. Electro-

cardiogram showed evidence of myocardial damage (Fig. 8). On a diet containing C., 150, P., 60, F., 75, she spilled 12 gm. in 24 hours. She was given 15 units of insulin once a day. There has been remarkable relief of her precordial symptoms in the face of the severe myocardial damage.

CASE 9.—Frieda B., aged 58, housewife, was first seen, September 8, 1930, complaining of marked weakness, polyuria, dryness of tongue, sleeplessness, headaches and frequent attacks of precordial pressure with palpitation and dyspnea, especially brought on by slight exertion. She had lost 40 pounds since the onset of her diabetes, 6 years ago. Examination disclosed a middle-aged woman, considerably wasted, evidence of hypertensive cardiac hypertrophy (confirmed by a 6-foot chest plate). There was a soft systolic blow over the base of the heart and a metallic accentuation of the aortic second sound. Her blood pressure was 210/110. She was excreting 40 gm. of sugar in 24 hours and her fasting blood sugar was 333 mg.%. Electrocardiogram (Fig. 9) showed evidence of myocardial damage. The patient was placed on a diet containing 225 gm. of available glucose, with 40 units of insulin in 2 divided doses. For the past 4 years she was maintained on this regimen, her weight has increased 15 pounds, she is always excreting between 5 and 10 gm. of sugar daily and her fasting blood sugars fluctuate between 200 and 270 mg.%. Although she still experiences symptoms of angina pectoris, they occur at relatively infrequent intervals and of a definitely milder order.

CASE 10.—Mitchell F., aged 43, discovered that he was diabetic in 1925. When seen, in June, 1927, he had no symptoms and examination disclosed a poorly nourished individual weighing 125 pounds, showing no other abnormal physical findings. He was then excreting traces of sugar and his fasting blood sugar was 160 mg.%. Blood pressure was 110/60. He was given a diet of C., 100, P., 60, F., 150, and no insulin. He was symptom-free until June, 1931, when he started to complain of attacks characterized by precordial pain and pressure radiating down both arms, paresthesias of the fingers, and dyspnea. These attacks were brought on by exertion and were relieved by rest. Examination of the heart disclosed no abnormalities. Blood pressure was 118/90. His urine was free of sugar and his fasting blood sugar was 164 mg.%. One year later he returned for another examination, at which time he reported that his anginal symptoms were becoming progressively worse and of greater frequency. He disclosed a definite break in sugar tolerance and his fasting blood sugar was 204 mg.%. Examination of his heart showed no abnormalities. His blood pressure was 128/86. His electrocardiogram was entirely normal. Teleoroentgenogram showed a heart normal in size, shape and position. A diagnosis was made of angina pectoris without coronary damage. He was then given a high carbohydrate diet consisting of C., 200, P., 60, F., 100, with 15 units of insulin twice a day. His diabetes was promptly controlled, for he excreted traces of sugar and his fasting blood sugars remained between 118 and 141 mg.%. He has been under observation for 3 years on a high-carbohydrate-insulin régime, during which time he has gained 7 pounds. He states that his anginal symptoms occur only rarely, are milder and are without radiations. His general well-being is much improved and he is able to engage in much more physical activity than he did before.

Discussion. In the consideration of the use of insulin as a therapeutic agent, the following principles were employed to protect the patient against even the mildest form of hypoglycemic reaction:

1. *Dietetic Control.* The caloric value of the diet was equivalent to the total energy requirements of the body and was computed on the basis of the sum of the basal heat production, the specific

dynamic action of the foodstuffs plus an estimated percentage of the basal metabolism to allow for activity. No attempt was made to reduce overweight patients because it was felt that a reducing diet would require too severe a restriction in carbohydrates.

Protein was given in the proportion of 1 gm. per kilo. of body weight. The amount of carbohydrate administered, influenced by our desire to give the patient an amount equal to the lower limits of what the normal person takes, that is, 250 gm., was never less than 3 gm. of carbohydrate per kilo of body weight. The fat was established by subtracting the caloric value of the protein and carbohydrates from the total calories and dividing the figure by 9, which is the caloric value of a gram of fat.

2. *Insulin.* Insulin was started in small test doses which were gradually increased up to the point where the sugar entirely disappeared from the urine or appeared only in traces. Blood sugars were not used as a criterion for the control of the diabetic state. It was felt that if a diet containing 200 or 250 gm. of available glucose could be taken care of by the organism without losing any in the urine, that the glucose was being either burnt or stored and that both these phenomena would relieve the clinical picture of this metabolic disorder.

3. *Further Dietetic Measures.* Realizing that the duration of the insulin effect in its depression of the blood sugar is in direct proportion to the dose of insulin, we instituted a routine protective procedure of giving our patients 15 gm. of readily absorbable carbohydrate (preferably in the form of fruit juice) 2 hours after the dose of insulin, which is the time when insulin shock is most likely to occur. We found this procedure so important that we routinely order the postcibal carbohydrate in all diabetics who take insulin. Since that is the time when the patient is experiencing a maximal insulin effect, we feel that this carbohydrate can be given with impunity. The result has been that hypoglycemic attacks have become an extreme rarity among our patients.

Some of these patients who were suffering from symptoms of coronary disease have been free of attacks for as long as 2 years since starting treatment. No attempt is being made to show that the use of insulin cures angina in these patients. Although the syndrome has entirely disappeared in many patients, others have been greatly relieved. None has been made worse by its use. We feel that this favorable clinical outcome is the result of having protected our patients against toxic insulin symptoms as manifested by hypoglycemic attacks.

These observations are not in accord with the clinical reports of Parsonnet and Hyman,[16] who have indicated that anginal symptoms are frequently aggravated in the insulin-treated cases even when the blood sugars are normal. They suspected that insulin has a toxic effect upon the myocardium regardless of its relationship to

the metabolism of glucose. On examination of their protocols, it will be seen that the blood sugar determinations were made several hours and even the following day after the attack of coronary thrombosis occurred. In some of the patients, glucose had been administered in the *interim*. We feel that these values have little significance regarding the content of sugar in the blood at the time the coronary episode occurred. Soskin and his co-workers feel that cardiac impairment, which both clinically and electrocardiographically resembles that produced by insulin hypoglycemia, may be produced in the elderly diabetic by giving therapeutic doses of insulin over a long period of time in spite of the fact that the blood sugars may be within the usually accepted normal range. An examination of their protocols reveals a condition, however, which does not warrant such conclusions. In citing their case of Harry S., for example, they record the fact that in spite of his maintaining an average blood sugar of 80 mg.%, while taking insulin, he showed electrocardiographic changes and cardiac symptoms similar to what they could produce in this patient by voluntarily eliciting a hypoglycemic attack. A detailed record of this patient's blood sugars on different days shows as follows: 61, 53 and 133 mg.%. Of course they will average 80 mg.%, but it is the cardiac picture which is created by a depression in the blood sugar to 61 and 53 mg.% that tells a clearer story. These are obviously hypoglycemic levels. Using the average of several figures, among which is included a high blood sugar, can only create an erroneous impression. It would be of considerably greater importance to determine the sugar content of the blood 3 and 4 hours after insulin has been injected in order to decide whether the patient is hypoglycemic. It is the lack of this type of observation that has led to what we consider false conclusions.

We feel also that a great deal of harm has been done by introducing the concept that insulin has a deleterious effect upon the heart of the elderly diabetic. It is unquestionably the hypoglycemic attack which is fraught with danger, but if it is possible to obviate the toxic effect of this hormone, why discard it as dangerous? Insulin is a double-edged sword much like any other powerful drug or hormone. Given in therapeutic doses it produces remarkable therapeutic effects; given in toxic doses it can even kill. But so is it true of morphin; one may give $\frac{1}{4}$ gr. for its desired effect and one may give 4 gr., enough to kill. Yet no one would think of eliminating morphin from his armamentarium because 4 gr. is a poison.

Conclusions. 1. The use of insulin in the diabetic suffering from angina pectoris and coronary sclerosis is discussed.

2. Insulin, like any other pharmacologic substance may be a toxic or a therapeutic agent, depending upon the manner of its use.

3. Methods for adequately protecting patients against the toxic effects of insulin are presented.

4. Insulin has been found to have a remarkable therapeutic value for the relief of cardiac pain of the diabetic.

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PRESENT VIEWS OF CALCIUM-PHOSPHORUS METABOLISM.*

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It is impossible to discuss the lesions resulting from abnormalities of calcium-phosphorus metabolism until the normal metabolism of these substances is known or hypothesized. The present state of our knowledge of calcium-phosphorus metabolism is so incomplete that it becomes necessary to construct from known data a workable hypothesis. This paper will attempt the elaboration of such an hypothesis from reported experimental and clinical data and from the results of personal investigation.

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Calcium and phosphorus enter the body by way of the diet. The normal daily intake of calcium is approximately 1 gm. and of phosphorus 2 gm. Although a normal amount of calcium and phosphorus may be ingested, yet this does not assure the assimilation of these elements and their entry into the body economy. Not only must an adequate supply of each element be present in the diet, but there must exist the proper quantitative proportion between calcium and phosphorus. The existence of a disproportion between the two is frequently as harmful as an absolute lack of either. Calcium should be in relation to phosphorus 1 to 1.5 or 1 to 2. Excessive dietary phosphorus, by forming insoluble compounds with the calcium of the diet, will markedly reduce the amount of calcium possible of absorption.

Quite frequently a large proportion of these elements occurs in the diet in insoluble forms and their assimilation by the gastrointestinal tract is consequently impossible.

The local conditions existing within the lumen of the small intestine may aid or deter the assimilation of calcium and phosphorus. Soluble salts of calcium may be thrown out of solution by the presence within the small intestine of excessive amounts of the carbonates of the digestive juices. The presence of excessive amounts of phosphates may act similarly; and a marked alkalin reaction of the intestinal contents may also precipitate soluble calcium salts and render them unassimilable. In the presence of large amounts of free fatty acids soluble calcium compounds are rendered insoluble through saponification. In consequence, excessive dietary fat, or the inability of the patient properly to digest the normal fat content of his diet (celiac disease) will, by rendering the dietary calcium insoluble, reduce the amount of this element available for assimilation.

Contrasted to these deterrent factors, assimilation of calcium and phosphorus is augmented by an adequate supply of vitamin D; by an acid reaction of the intestinal contents; and by a systemic acidosis—such as may be produced by the administration of ammonium chlorid.

The amount of ingested calcium phosphorus which is daily absorbed from the small intestine is not known but apparently varies widely in various individuals and at different times within the same individual. The quantitative intake of calcium and phosphorus may be quite adequate, but through faulty assimilation the amount of these elements reaching the tissues of the body may be inadequate.

Naturally those portions of the ingested calcium and phosphorus which are not assimilated are excreted. To this excretion of the unassimilated calcium and phosphorus must be added that portion of these elements which are thrown out from the blood stream. Normally 90% of the excretion is by way of the feces and 10% by

way of the urine. In normal adults the total amounts excreted in 24 hours, as estimated in periods of days, are slightly less than the amounts of these elements ingested during the same period of time.

Calcium and phosphorus assimilated from the small intestine enter the plasma of the blood. The total calcium content of the serum is normally in a concentration of 10 mg. % and inorganic phosphorus in a concentration of 4 mg. %. In a chemical sense the blood serum content of calcium is regarded as a saturated solution; certainly as regards neutral calcium phosphate the serum is saturated. The blood serum, however, does not behave in the unstable manner expected of a saturated solution.

The total blood serum calcium is divided into three fractions:

(*a*) The first fraction represents a loose colloidal combination with serum protein. This fraction totals approximately 4 mg. %, is physiologically inactive and comprises the fraction which is most stable and undergoes the least fluctuation in concentration.

(*b*) The second fraction represents a chemical combination of calcium with phosphorus in the form of a salt solution. The concentration of this fraction amounts to approximately 4 to 5 mg. % and is physiologically active. It is believed that the solution of this fraction is maintained through the intermediary action of parathyroid hormone and, according to Aub, brings the normal blood serum level of calcium above the renal threshold for this element and maintains it there.

(*c*) The third fraction, amounting to 1 to 2 mg. %, is present in the form of ionized calcium and is physiologically active.

Of the above three fractions, the last two are in equilibrium with phosphorus. Of the total calcium in the blood serum but 40 to 60% is diffusible.

It is important that the various fractions of blood serum calcium be determined. Abnormality of calcium metabolism is reflected more promptly in variations of the quantitative amount of either the ionized fraction or the second fraction, that held in solution through the action of parathyroid hormone. It is necessary to determine the total amount of blood protein, and consequently of protein metabolism, so that the calcium fraction in colloidal combination with the serum protein may be accurately known.

There is a demonstrable reciprocal relationship between the calcium and phosphorus content of the blood serum. If one rises, the other must fall if they are to remain in solution. Phosphorus exercises an important control in the maintenance of calcium solubility in the blood serum. The attempt is made to maintain the calcium-phosphorus concentration within the blood serum at a normal level. If it is not possible to obtain additional molecules from the diet, then the deposits in the bones will be drawn upon. Alteration in the normal concentration of these elements within the blood serum, resulting from abnormalities of excretion, vitamin D

content, or parathyroid hormone secretion, are not to be considered at this point.

It is possibly correct to regard the blood serum, calcium and phosphorus as being in a state of transportation either to or from the body tissues. It seems quite unlikely that the blood itself, although a circulating tissue, is actively engaged in the metabolism of these two elements. (This view is open to criticism.) The calcium and phosphorus of the blood serum are carried to the various organs and tissues of the body to perform their allotted functions.

Soluble calcium salts (by converting prothrombin into thrombin) are essential to the clotting of blood. Calcium is essential for the contractibility of involuntary muscle and for the maintenance of a normal degree of neuromuscular irritability. It also exerts a dominant rôle in maintaining the selective permeability of the living cell. Phosphorus is essential to lipoid metabolism, to the energizing of muscular contraction, and, in an unknown manner, is apparently essential to the functioning of nerve tissue. As approximately 99% of the body calcium is present within the bones, the most important function of these two elements consists in their deposition within the skeletal system of the body. Particularly is this true in the young and growing individual, as the strength and integrity of the bones depends upon the adequate performance of this function.

The manner in which calcium and phosphorus are removed from the blood stream, pass to the tissue fluids and are finally deposited in the form of tricalcium phosphate within the osteoid tissue of bones, comprises one of the great gaps in our knowledge of the metabolism of these two elements. There are two views regarding the manner in which calcium and phosphorus permeate and are precipitated in osteoid tissue. One is that this transportation and precipitation takes place through the medium of specific cells—the osteoblasts; the other view holds that the permeation and precipitation is one of a chemical nature and is, for the most part, independent of cellular activity.

Two substances play an important part in the precipitation of these elements in the osteoid tissue. The first is the enzyme *phosphatase* which, being the product of cellular activity, is probably elaborated, in varying degrees, by all cells of the body. The second substances, vitamin D, plays a most important part in this precipitation. Attention should be called, at this point, to the fact that vitamin D is supplied from two sources: (1) Through the diet; (2) through elaboration within the body of the individual. In the second case certain of the ultraviolet rays of the sunlight, act upon cholesterol-like compounds within the skin of the individual. These compounds, through the action of the ultraviolet rays, undergo a spatial rearrangement of their molecules and are transformed into vitamin D.

Phosphatase is possibly activated by vitamin D, and through enzymic action, has, according to Kay, the power of converting the

calcium-phosphate esters of the blood into insoluble tricalcium phosphate which is precipitated as such in the osteoid tissue. Such precipitation is aided by an alkalin balance or by an increase of the local phosphorus. Calcification is also found to vary inversely to the blood volume flow.

Calcium occurs in the bones in the proportion of 3 molecules of tricalcium phosphate to 1 molecule of calcium carbonate. This proportion persists regardless of whether calcium is being deposited or withdrawn from the bone. (75% of the ash of the entire body and 85% of the mineral matter of the bones is composed of calcium phosphate.)

Although calcium is deposited in all parts of the bony skeleton, Aub has shown it can be most easily mobilized and withdrawn from the spongiosa of the long bones. Such arrangement permits of the normal withdrawal of necessary amounts of calcium with a minimum impairment of the structural strength of the bones. It seems likely that calcium may be withdrawn from these depots more readily than it can be obtained by assimilation from the diet. Such limitation does not hold when pathological decalcification is operative.

Sight must not be lost of the fact that but two tissues normally calcify—bone and teeth. Experimentation has shown that these two tissues are the only ones which will undergo *in vitro* calcification. The calcification so produced closely resembles *in vivo* calcification. It must hence be concluded that bones and teeth possess over all other tissues a specific affinity for the calcium-phosphorus combination.

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF VITAMIN B (B_1) TO POLYNEURITIS IN THE ALCOHOL ADDICT.*

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It is well known that alcohol addicts who consume little food often develop marked neurologic changes, whereas those who eat well, and in whom assimilation is not impaired by gastro-intestinal

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or hepatic disorders, rarely develop neurologic symptoms. Prior to the realization of the rôle played by the vitamins, it was thought that a full diet prevented the direct neurotoxic action of alcohol. That vitamin deficiency may be a factor in the development of polyneuritis in the alcohol addict was first mentioned, on theoretical grounds, by Shattuck[1] in 1928, and by Minot[2] in 1929; but Wechsler[3] was the first to analyze qualitatively the dietary histories of alcohol addicts with polyneuritis. He concluded that avitaminosis played a definite, and possibly the decisive, rôle in the production of polyneuritis. Meyer[4] also studied several alcohol addicts, with the concept of avitaminosis in mind, and came to similar conclusions. Following Wechsler's preliminary report Minot, Strauss and Cobb[5] analyzed qualitatively the diets of 43 alcohol addicts with polyneuritis. In 41 subjects the diet was considered inadequate. They stressed the importance of the inadequate food intake, and the rôle played by disorders of the gastro-intestinal tract in conditioning the assimilation and utilization of the accessory food factors. They pointed out the similarity of the manifestations of beriberi and polyneuritis in the alcohol addict, and suggested a common etiologic factor, namely, the lack of vitamin B. Strauss,[6] in 1935, gave a pint to a quart of blended whiskey daily to each of 10 alcohol addicts with polyneuritis; in addition a vitamin-rich diet was given, supplemented by the oral administration of 18 gm. of Vegex or 90 gm. of brewer's yeast, and 10 cc. of a vitamin B_1 concentrate administered parenterally, with 10 cc. of liver extract parenterally at weekly intervals. On this régime Strauss observed that the peripheral neuritis improved as rapidly with alcohol as without it. From this evidence he concluded that ingestion of whiskey had no demonstrable toxic effect on the peripheral nerves.

From the above literature on the etiology of polyneuritis in alcohol addicts it has been demonstrated:

1. That the alcohol addict with polyneuritis has as a rule a qualitatively inadequate food and vitamin intake.[3, 5]

2. That assimilation or utilization of the accessory food factors is often impaired by gastro-intestinal or hepatic disorders.[3, 5]

3. That the clinical manifestations and the pathologic findings of "alcoholic" polyneuritis and beriberi are remarkably similar.[5]

4. That ingestion of large amounts of whiskey, when accompanied by a vitamin-rich diet, supplemented by vitamins administered parenterally and per os, has no direct neurotoxic action.[6]

To complete the evidence, however, that polyneuritis* in the alcohol addict is due to the lack of vitamin B, the following postulates should be fulfilled: 1. It should be shown that the diet consumed by alcohol addicts with polyneuritis failed quantitatively, and over

* We are cognizant of the fact that there are other etiologic factors than avitaminosis B that may cause polyneuritis. These may and do operate in the alcohol addict as in subjects not addicted to the use of alcohol.

a sufficient period of time, to contain adequate amounts of vitamin B as compared with the normal requirement. 2. It should be shown that the diet consumed by alcohol addicts without polyneuritis, though the addiction was of long duration, contained quantitatively adequate amounts of vitamin B. This paper reports a series of quantitative observations bearing on the above points.

The vitamin B requirement of man has been estimated by Cowgill[7] from data on mice, rats, pigeons and dogs by the following formula:

$$\frac{\text{VITAMIN B mg. equivalent}}{\text{CALORIES}} = 0.0000284 \text{ WEIGHT in gm.}$$

We have applied Cowgill's method in a quantitative study of the diets of alcohol addicts to estimate their vitamin B and caloric intake. The values thus calculated were compared first, with the predicted requirement, and second, with the neurologic changes exhibited by these subjects. Cowgill has tested his formula by computing the vitamin B and caloric content of numerous human diets, associated and not associated with beriberi, and found a close agreement between the theoretical requirement predicted by his formula and the presence or absence of the disease. Examination of the Cowgill formula indicates that the vitamin B requirement is proportional to both the caloric intake and the body weight. From the nature of the equation, the expression

$$\frac{\text{VITAMIN B mg. equivalent}}{\text{CALORIES}}$$

(hereafter referred to as the VIT/CAL ratio) may be used as a quantitative expression, by reference to Cowgill's prediction chart,[7] of the adequacy or inadequacy of the vitamin B content of the diet of an individual of known weight. Cowgill uses caloric intake to express for practical purposes the energy exchange of an individual. The almost complete utilization by man of moderate amounts of alcohol is well known.[8] The energy exchange, however, calculated for practical purposes from the caloric intake, may not reasonably indicate the calories utilized when large quantities of alcohol are consumed, since under these conditions significant portions of alcohol may be excreted unchanged through the lungs and kidneys, or lost by vomiting and diarrhea. Moreover, the metabolic limits of the body to burn alcohol may be exceeded in subjects consuming more than a pint of whiskey daily, since Mellanby[9] has calculated that the average man can oxidize but 10 cc. of alcohol per hour.

The importance of the calories derived from alcohol in relation to vitamin B requirement can be illustrated by using Cowgill's calculation of the VIT/CAL ratio of Sherman's[10] average American diet. This diet contains 6847 mg. eq. of vitamin B and 2500 calories, and gives a VIT/CAL ratio of 2.74. This ratio, by reference to Cowgill's prediction chart, is adequate for a 96 kg. man. An indi-

vidual who supplements this diet by one pint of whiskey daily adds about 1600 calories to the denominator of the equation. The VIT/CAL ratio now becomes 1.67, which is adequate for a 60 kg. man. An individual weighing more than 60 kg. on this vitamin B and caloric consumption would, theoretically, in time show evidence of a vitamin B deficiency.

To calculate the VIT/CAL ratio of the diets of our subjects we used Cowgill's[7] Vitamin B (B_1) Index of Foods, which also lists the caloric values. Average portion weights[11] were used to estimate the consumption in grams of portions of various foods consumed. Fortunately for our calculations the diets of confirmed alcohol addicts are as a rule monotonous and simple, and less error results in the estimation of these diets than in the determination of the VIT/CAL ratios of persons consuming a full, varied, and mixed diet.

The 42 subjects forming the basis of this study were tentatively selected on the probability of the patient giving an adequate and accurate history of the dietary and alcoholic intake. If the patient gave essentially the same history on several succeeding days (only about 1 in 10 alcohol addicts did this), and if from information given by friends or relatives the history seemed reliable, then the case was accepted for this study.* Two VIT/CAL ratios were calculated for each patient, one omitting (VIT/CAL without ALC.) and one including (VIT/CAL with ALC.) the calories derived from alcohol. In subjects consuming more than a pint of whiskey daily, a third ratio was calculated which included only the first 1600 calories derived from alcohol per diem as this is the probable maximum amount that can be oxidized (VIT/CAL + 1600). Each ratio was compared with the predicted requirement, and with the neurologic observations made before treatment was instituted. It is recognized that the alcohol addicts forming the basis of this study often manifested signs attributable to an avitaminosis other than B. At the present time, however, there is no method to estimate quantitatively the human requirement of these other vitamins. It was therefore impossible for us to correlate quantitatively the intake of vitamins other than B with the clinical findings in our subjects.

We have included in this study two groups of subjects: those definitely having polyneuritis and those definitely not having polyneuritis. Subjects included in the group having polyneuritis had at least absent ankle jerks and demonstrable sensory changes in the peripheral nerves. Most subjects in this group showed more than this minimal requirement. Subjects to be included in the group without polyneuritis had no changes in the deep reflexes and showed no sensory changes. Certain subjects showing changes

* In the sense that only alcohol addicts who gave reliable histories were included in this study our cases are selected. However, these cases represent consecutive subjects admitted to the Medical Service fulfilling the criteria for the diagnosis of polyneuritis who, according to our criteria, gave reliable histories.

falling between these two groups of criteria were excluded from the study.

TABLE 1.—SUMMARY OF OBSERVATIONS ON 26 ALCOHOL ADDICTS WITH POLYNEURITIS.

				Alcohol	Food: average daily consumption in—		VIT/CAL ratios				Neurologic involvement		
Case	Sex	Age	Time	Average daily intake in calories	Calories	Vit. B mg. ca	Without alcohol	+ 1660 C.	With alcohol	Cowgill's predicted requirement	Polyneuritis	Cord.	Brain
258	M	51	1 Y	6,400	405	1,317	3.2	0.6	0.2	1.75	+	0	0
259	M	41	6 M	3,200	755	1,725	2.3	0.7	0.5	2.35	+	0	0
271	M	37	3 Y	1,600	330	923	2.8	0.5	0.5	1.80	+	+	+
273	M	50	25 Y	1,600	2,500	6,874	2.7	1.7	1.7	1.80	+	+	+
279	F	45	7 Y	1,600	833	2,286	2.7	0.9	0.9	1.25	+	+	+
280	M	57	3 M	6,400	888	1,845	2.0	0.7	0.3	2.00	+	0	0
295	M	59	10 W	1,600	673	1,020	1.5	0.4	0.4	1.70	+	0	0
297	M	38	2 M	1,600	1,250	3,423	2.7	1.3	1.3	2.00	+	0	0
300	M	53	3 M	4,800	357	978	2.7	0.5	0.2	2.15	+	+	0
324	M	48	6 M	1,600	965	3,130	3.2	1.2	1.2	1.85	+	0	+
327	M	43	2 M	6,400	0	0	0	0	0	2.20	+	0	0
333	M	40	2 M	4,500	0	0	0	0	0	1.90	+	+	+
335	M	52	2 M	800	756	1,624	2.1	...	1.0	1.71	+	0	0
336	M	56	33 D	4,800	863	2,431	2.8	1.0	0.4	2.35	+	0	0
339	F	45	2 Y	1,600	492	406	0.8	0.2	0.2	1.40	+	+	0
366	M	52	22 D	3,000	500	1,800	3.6	0.9	0.2	2.55	+	0	0
388	M	47	8 M	4,000	1,121	2,590	2.3	0.9	0.7	1.15	+	0	0
392	F	57	2 M	2,600	276	671	2.4	0.4	0.2	2.05	+	0	+
443	M	35	6 W	2,400	2,018	5,932	2.9	1.6	1.3	2.20	+	+	+
444	M	29	8 Y	3,200	1,809	5,774	3.2	1.7	1.1	1.80	+	+	+
457	M	38	2 M	3,200	1,102	3,825	3.5	1.0	0.9	1.70	+	0	0
458	M	54	15 D	3,200	555	1,107	2.0	0.5	0.3	2.10	+	0	0
459	M	46	20 D	3,200	726	3,355	4.6	1.4	0.7	2.10	+	0	0
467	M	45	3 W	4,800	0	0	0	0	0	1.85	+	0	+
468	F	47	10 Y	2,400	1,568	2,878	1.8	0.9	0.7	2.30	+	0	+
472	M	46	6 Y	2,400	720	3,000	4.2	1.3	1.0	1.60	+	0	0

Results. In line with the hypothesis that polyneuritis in the alcohol addicts is due to lack of vitamin B, we find that the diet consumed by those alcohol addicts with polyneuritis failed quantitatively, and over a sufficient period of time, to contain adequate amounts of vitamin B as compared with the predicted requirement. The evidence for this conclusion is presented in Table 1, which presents data on 26 subjects. It will be noted that in these alcohol addicts an adequate or an inadequate diet in respect to vitamin B as estimated by the VIT/CAL without ALC. ratio bears no relationship to the presence or absence of polyneuritis. In 18 subjects the diet alone was adequate when considered in relationship to the vitamin B requirement as calculated on the basis of food alone. Since, however, in these subjects a large percentage of the energy intake

was represented by alcohol, the calories obtained from this source should be included in the equation. When all the available calories are included (VIT/CAL with ALC. ratio) the vitamin B intake became in every instance inadequate. Since 18 of these 26 subjects consumed more than 1600 alcohol calories daily, and thereby probably exceeded the metabolic limits of the body to burn alcohol, the VIT/CAL + 1600 ratio may be the most representative ratio for this group. In the 18 subjects to whom this formula was applicable every one remained inadequate in vitamin B intake as judged by Cowgill's predicted requirement.

TABLE 2.—SUMMARY OF OBSERVATIONS ON 8 ALCOHOL ADDICTS WITHOUT POLYNEURITIS WHO MAINTAINED AN ADEQUATE VITAMIN B INTAKE.

			Alcohol.		Food: average daily consumption in—		VIT/CAL ratios.				Neurologic involvement		
Case.	Sex.	Age.	Time.	Average daily intake in calories.	Calories.	Vit. B mg. eq.	Without alcohol.	+ 1600 C.	With alcohol.	Cowgill's predicted requirement.	Polyneuritis.	Cord.	Brain.
330	M	61	40 Y	450	2,500	7,890	3.1	..	2.7	2.25	0	0	0
334	M	64	40 Y	1,500	2,083	10,398	5.0	..	2.8	2.75	0	0	0
340	F	43	6 M	1,600	3,272	9,918	3.0	2.0	2.0	1.70	0	0	0
358	M	45	18 M	750	1,901	7,100	3.7	..	2.7	2.60	0	0	0
403	M	35	7 Y	800	5,021	17,784	3.5	..	3.0	2.67	0	0	0
417	M	55	10 Y	1,600	2,457	10,466	4.3	2.6	2.6	2.25	0	0	0
455	M	34	7 Y	1,600	2,868	12,102	4.2	2.7	2.7	2.00	0	0	0
466	M	54	10 Y	2,300	3,387	13,404	3.9	2.7	2.3	1.70	0	0	0

On the other hand, the diet consumed by alcohol addicts without polyneuritis, though the addiction was of long duration, contained quantitatively adequate amounts of vitamin B as compared with the normal requirement. The evidence on which this conclusion is based is given in Table 2, where data on 8 subjects without polyneuritis are tabulated. These subjects maintained an adequate intake of vitamin B even though they were on a daily consumption of alcohol varying from 450 to 2300 calories over periods ranging from 6 months to 40 years. In every instance the VIT/CAL without ALC. ratio exceeded by a substantial margin the predicted requirement, and even when the alcohol calories are included in the calculation the diet remained adequate in respect to vitamin B. Each of these subjects regularly included in their diets a food that provided exceptional amounts of vitamin B. Sherman's[10] average American diet was estimated by Cowgill to have a VIT/CAL ratio of 2.74. Each of these subjects maintained a VIT/CAL without ALC. ratio of 3 to 5. Subject 334, aged 64 years, has been a bartender since the age of 24. During this 40-year period his average consumption of

alcohol has consisted of 10 1½-ounce drinks of whiskey daily; the whiskey was placed in a 10-ounce bar glass which was then filled with whole milk, and in this way the patient obtained at least 75 ounces of milk daily. This amount of milk contains about 1500 calories and about 8100 mg. eq. of vitamin B. By adding the 1500 alcohol calories to the 1500 milk calories we obtain a VIT/CAL with ALC. ratio of 2.7. The additional food he consumed maintained his VIT/CAL with ALC. ratio at 2.85, which just exceeded his predicted requirement of 2.75. Subject 403 obtained an extremely high intake of vitamin B by eating regularly 5 eggs and 2 slices of ham for breakfast, and 2 pork chops and bean or pea soup for lunch. These foods are all exceptionally rich sources of vitamin B.*

TABLE 3.—SUMMARY OF OBSERVATIONS ON 8 ALCOHOL ADDICTS WITHOUT POLYNEURITIS WHO CONSUMED INADEQUATE AMOUNTS OF VITAMIN B.

			Alcohol		Food: average daily consumption in—		VIT/CAL ratios.				Neurologic involvement.		
Case.	Sex.	Age.	Time.	Average daily intake in calories	Calories	Vit. B mg. eq.	Without alcohol	+ 1600 C.	With alcohol	Cowgill's predicted requirement	Polyneuritis.	Cord.	Brain.
325	F	35	14 D	1,600	2,500	6,800	2.7	1.6	1.6	1.70	0	0	0
359	M	52	7 D	3,200	112	100	0.9	0.06	0.03	2.30	0	0	0
363	M	63	14 D	4,800	0	0	0	0	0	2.15	0	0	0
357	M	20	18 D	3,200	640	2,199	3.4	1.0	0.6	2.35	0	0	0
402	M	30	6 M	1,600	2,165	7,413	3.4	2.0	2.0	2.10	0	0	0
413	M	50	10 D	2,400	638	2,000	3.1	0.9	0.7	2.40	0	0	0
438	M	48	21 D	6,400	412	660	1.6	0.3	0.1	1.80	0	0	0
456	M	48	2 M	3,200	1,445	5,667	3.9	1.8	1.2	1.80	0	0	0

The 8 subjects listed in Table 3 were all deficient in vitamin B intake as judged by the VIT/CAL with ALC. ratio. As judged by the VIT/CAL + 1600 ratio, 7 of these 8 subjects were deficient. The exception (Subject 456) had a borderline ratio. The protective factor in this group was the short duration of the alcoholic bout. In 6 of the 8 subjects the period of alcohol addiction did not last over 3 weeks. Subject 402 was on an alcoholic bout for 6 months with an average consumption of 1 pint of whiskey daily. His predicted requirement as judged by the VIT/CAL ratio was 2.1. The estimated VIT/CAL with ALC. ratio was 2, which falls within Cowgill's borderline range. Subject 456 was on an alcoholic bout for 2 months with an average consumption of 1 quart of whiskey daily. His predicted requirement by the VIT/CAL ratio was 1.8. The estimated

* Even if the error involved in the estimation of the diets of the subjects presented in Tables 1 and 2 were as high as 50%, the Vit/Cal +1600 ratio of only one subject (334) would conflict with our postulates.

VIT/CAL + 1600 ratio was 1.8. If all the alcohol calories are included, the estimated VIT/CAL with ALC. ratio becomes 1.2, which is definitely inadequate. This individual, as will be shown later, with this degree of vitamin B deficiency as measured by this latter ratio and over this period of time, would not with certainty develop polyneuritis.

The time required to produce clinical evidence of polyneuritis on a vitamin B deficient diet is variable. That the disease may develop in a short time is demonstrated by 4 subjects (458, 459, 366 and 336), all of whom had polyneuritis on admission following a period of vitamin B deficiency lasting 15, 20, 22 and 33 days, respectively. We were able to date accurately the duration in 3 of these subjects since they began their drinking bout on Christmas or New Year's Eve. The other subjects having polyneuritis were on a continuous daily consumption of whiskey varying from 6 weeks to 25 years. It is reasonable to assume that a subject having a VIT/CAL ratio equivalent to but 30% of the predicted requirement would develop clinical evidence of vitamin B deficiency earlier than a subject having 60% of the predicted requirement. Ohomori[12] found signs of nerve involvement as early as the 7th to 10th day on a diet estimated by Cowgill's method to be 36% adequate. We have estimated the number of days of complete 100% deficiency by multiplying the per cent deficiency by the number of days over which the deficiency occurred (hereafter referred to as "days of estimated absolute deficiency"). In 10 days Ohomori's subjects accumulated 6.4 days of estimated absolute deficiency of vitamin B. Frazer and Stanton[13] fed a diet 68% adequate as judged by the VIT/CAL ratio to a group of laborers whose average requirement was a ratio of 1.25. The first case of beriberi appeared on the 89th day, or following 28.5 days of estimated absolute deficiency. We have calculated the days of estimated absolute deficiency in each of our subjects. In those subjects using more than 1600 alcohol calories daily the VIT/CAL + 1600 ratio was used in the determination. Each subject with an estimated absolute deficiency of 21 days or more had polyneuritis. Since many subjects in this group may have had signs of peripheral neuritis for a variable length of time before observation, we have tabulated in Table 4 only the subjects who had estimated absolute deficiency for 21 days or less. Subject 459 developed polyneuritis after 6.6 days of estimated absolute deficiency, while Subject 438 showed no clinical evidence of polyneuritis after 17.4 days of estimated absolute deficiency. Polyneuritis was present in Subjects 458, 366 and 336 after 11.4, 14.3 and 19.1 days, respectively, of estimated absolute deficiency. It appears, therefore, that an individual may develop polyneuritis if the caloric need is satisfied by a diet free of vitamin B for a period of a week, while every individual in our series had polyneuritis if the period of estimated absolute deficiency was 21 days or more.

Subject 456, without polyneuritis, is the only possible exception to the rule that an alcohol addict with an inadequate vitamin B intake over a sufficient period of time will develop polyneuritis. This subject consumed a diet just adequate, as expressed by the VIT/CAL + 1600 ratio, and therefore, on this basis, is not an exception. If all the alcohol calories are included in the denominator of the equation (a procedure which we do not feel to be justified, as 1600 alcohol calories is the probable maximum amount metabolized within 24 hours), the VIT/CAL with ALC. ratio becomes 1.2, which is 33% less than his predicted requirement of 1.8. On this basis the deficiency lasted only 60 days, giving 19.8 days of estimated absolute deficiency. It appears that this duration of vitamin B deficiency will not with certainty produce polyneuritis.

TABLE 4.—CORRELATION OF DAYS OF ESTIMATED ABSOLUTE DEFICIENCY IN VITAMIN B AND POLYNEURITIS IN THE ALCOHOL ADDICT.

Subject.	Estimated deficiency in %.	Duration of deficiency in days.	Estimated absolute deficiency in days.	Polyneuritis.
325	6.0	14	0.8	0
413	63.0	10	6.3	0
459	33.0	20	6.6	+
359	96.0	7	6.7	0
402	5.0	180	9.0	0
357	57.0	18	10.2	0
458	76.0	15	11.4	+
363	100.0	14	14.0	0
366	65.0	22	14.3	+
438	83.0	21	17.4	0
336	57.0	33	19.1	+
467	100.0	21	21.0	+
297	35.0	60	21.0	+

Discussion. The etiology of polyneuritis in the alcohol addict is clarified by the quantitative estimation of the adequacy or inadequacy of the vitamin B intake of alcohol addicts. The fact that every alcohol addict with polyneuritis had a VIT/CAL with ALC. or VIT/CAL + 1600 ratio below the predicted requirement for this vitamin is in itself good evidence that the lack of vitamin B is the cause of the polyneuritis. This fact alone, however, is not direct and conclusive evidence. It is possible that the polyneuritis in the alcohol addict may be due to the direct toxic action of alcohol or even to the lack of another vitamin, such as vitamin A, as suggested by Mellanby,[14] and the inadequate intake of vitamin B may be coincidental because of anorexia. Evidence, in addition to that of Strauss,[6] that alcohol does not have a direct toxic action on the peripheral nerves is derived from the fact that no alcohol addict with an adequate vitamin B intake, as expressed by the VIT/CAL with ALC. ratio, had clinical evidence of peripheral neuritis. It is true that the group without polyneuritis but with an adequate vitamin B intake (Table 2) had an average per diem intake of whiskey less

than the group with polyneuritis. These subjects, however, drank an amount of whiskey sufficient to cause polyneuritis if alcohol *per se* were its cause. To illustrate this point, 4 subjects having VIT/CAL with ALC. ratios above the predicted requirement used whiskey over a long period of time without developing polyneuritis. Of these, 3 subjects (340, 417, 454) used 1 pint of whiskey daily for 6 months to 10 years, and 1 subject (466) used 23 ounces of whiskey daily for 10 years. That this is a sufficient intake of whiskey, and continued over an adequate period of time, to cause polyneuritis if alcohol had a direct neurotoxic action, is evidenced by the 3 subjects (297, 295, 335) with inadequate VIT/CAL with ALC. ratios who drank but 1 pint or less of whiskey daily for 10 weeks or less and developed polyneuritis. Subject 335, with an inadequate VIT/CAL with ALC. ratio, drank but ½ pint of whiskey daily for 2 months and developed polyneuritis. The 8 subjects with adequate VIT/CAL with ALC. ratios all drank ½ pint or more of whiskey daily for 6 months to 40 years without developing polyneuritis. It is therefore clear that in these subjects alcohol *per se*, even when used in large amounts over a long period of time, had no direct toxic action on the peripheral nerves.

The proof that polyneuritis in the alcohol addict and in beriberi are due to vitamin B deficiency rests upon the same evidence. Both diseases have been shown to occur only in subjects having a vitamin B intake less than their predicted requirement. Neither disease occurs in subjects having a vitamin B intake greater than their predicted requirement, unless their requirement is abnormally increased (fever, hyperthyroidism, pregnancy, diuresis) or assimilation is prevented (vomiting, diarrhea). Both diseases have similar clinical manifestations, and are characterized by similar pathologic findings. Both diseases, unless far advanced and the nerve lesions beyond repair, respond to adequate vitamin B therapy. We are therefore of the opinion that polyneuritis in the alcohol addict and beriberi are one and the same disease, and that both are due to the lack of vitamin B.

It is suggested that the alcohol addict, to prevent a possible polyneuritis, should consume a full mixed diet supplemented by about 250 mg. eq. (50 Sherman units) of vitamin B for each 100 calories of alcohol (about 1 ounce of whiskey) he consumes. This amount of vitamin B can be conveniently obtained in about 1 gm. of Vegex.

The lack of other accessory food elements, such as vitamin A, in association with the lack of vitamin B, as suggested by Mellanby,[14] does not seem to us to play a very decisive rôle in the production of polyneuritis in the alcohol addict. The vitamin A requirement of human beings at present is unknown. The estimation of the adequacy or inadequacy of the vitamin A intake in our subjects could be only conjecture. It is barely possible that each of our subjects deficient in vitamin B was also deficient in vitamin A.

This is not at all probable as in many of our subjects the period of alcohol addiction and food inadequacy was relatively short. Animals maintained on a diet deficient only in vitamin A require long periods of inadequacy before neurologic signs or symptoms become manifest. Conversely animals deficient in vitamin B develop neurologic changes relatively early. Polyneuritic signs in our subjects were always present after 21 days, and occurred as early as in 7 days of estimated absolute deficiency. This is probably too early to expect signs of vitamin A deficiency.

There was in our subjects no very clear correlation between the degree of vitamin B deficiency and the presence or absence of central nervous system involvement. In the 12 subjects showing central nervous involvement, 10 had an estimated absolute deficiency for 48 days or more. Subjects 443 and 467 showed signs of central nervous involvement after only 11.3 and 21 days, respectively, of estimated absolute deficiency. But other subjects may have an estimated absolute deficiency for longer periods of time without showing evidence of central nervous system involvement. Subjects, 472, 258 and 259, had 415, 240 and 126 days, respectively, of estimated absolute deficiency, but showed only peripheral nerve involvement. Although the changes in the central nervous system appeared clinically to be associated with vitamin B deficiency, there is clearly no correlation between the degree of deficiency of vitamin B and the presence or absence of spinal cord or brain involvement.

Summary. The vitamin B and caloric intake of 42 alcohol addicts, 26 of whom had polyneuritis, have been estimated quantitatively by Cowgill's formula. When the first 1600 calories contained in the alcohol consumed by each subject are included in the estimation of the VIT/CAL ratio, a definite correlation is found between the inadequacy or adequacy of the vitamin B intake and the presence or absence of polyneuritis. This correlation is as follows:

1. Every alcohol addict with polyneuritis had an estimated inadequate vitamin B intake.
2. No alcohol addict with an estimated adequate vitamin B intake had polyneuritis.
3. Every alcohol addict with estimated absolute deficiency of vitamin B for 21 days or more had polyneuritis.
4. Polyneuritis may develop in an alcohol addict as early as the 7th day of estimated absolute deficiency of vitamin B.

Our data substantiate the hypothesis that polyneuritis in the alcohol addict is due to the lack of vitamin B by demonstrating: (1) that the diet consumed by alcohol addicts with polyneuritis failed quantitatively and over a sufficient period of time to contain adequate amounts of vitamin B as compared with the predicted requirement; and (2) that the diet consumed by alcohol addicts without polyneuritis, though the addiction was of long duration,

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contained quantitatively adequate amounts of vitamin B as compared with the predicted requirement.

It is therefore concluded that alcohol has no direct toxic action (chronic) on the peripheral nerves, and that polyneuritis in the alcohol addict is due to vitamin B deficiency.

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A STUDY OF THE DIURETIC EFFECT OF MERCUPURIN IN MAN.*

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Since the introduction of novasurol as a mercurial diuretic by Saxl and Heilig,[1] in 1920, attempts have been made to vary the organic portion of the compound in its relationship to mercury in

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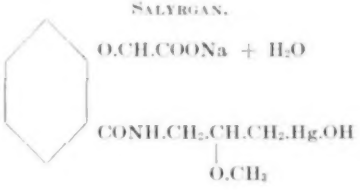
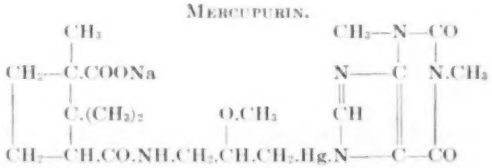
order to increase its efficiency and to decrease the general and local toxicity. Thus salyrgan, introduced in 1924 by Bernheim,[2] was found to have greater diuretic action and to be less toxic than novasurol.[3]

In 1928 v. Issekutz and v. Vegh[4] studied the diuretic action of numerous mercurial salts in rabbits and their toxicity in rats and found that preparation VI, a camphoric acid derivative, to be 10 to 15 times less toxic than sublimate and one-half as toxic as salyrgan. When combined with theophyllin, the diuresis was not only greater than that produced by salyrgan alone or salyrgan with theophyllin, but also retained the same relationship of toxicity as above. A combination closely resembling preparation VI was introduced clinically as novurit and is known in this country as mercupurin. This is a complex mercurial salt containing 5% theophyllin, 3.5% of which is claimed by the distributors[5] to be chemically bound to it. The essential differences between mercupurin and salyrgan can be seen from an examination of their chemical formulæ.

SALYRGAN.



MERCUPURIN.



The allylamid group, although alike in both preparations, separates the mercury from a cyclopentane in mercupurin, and from a benzol ring in salyrgan.

European investigators[6] in general have reported favorable clinical results with the use of mercupurin. In this country Crawford and McDaniel[7] obtained in every instance but one a greater diuresis with this drug than with salyrgan. On the other hand, although Fulton and Bryan[8] found that clinically mercupurin was an effective diuretic they concluded that no preference could be given to it over salyrgan.

The conclusion one reaches from a survey of the literature is that mercupurin seems to be an effective and probably a safe diuretic, but that there is still some doubt as to whether the presence of theophyllin in it makes it a more efficient diuretic than the simple mercurials.

The present study was planned to determine the efficiency and degree of safety of mercupurin as a diuretic in man and secondly to determine, if possible, whether the presence of theophyllin was necessary.

Methods and Results. Patients in congestive heart failure with considerable dependent edema were chosen for this study. All were kept on a preliminary control period of absolute bed rest before any diuretic was administered. The diet averaged 2700 calories and consisted of C. 240 gm., P. 90 gm., F. 108 gm. with a daily salt intake of approximately 5 gm. This salt content is considerably higher than that used by previous investigators. It has been shown that occasionally the effectiveness of a diuretic diminishes after its prolonged use, probably the result of depletion of the ions necessary to maintain ionic equilibria in the body.[9,10] There exists a definite relationship between the amount of fluid mobilized for diuresis and the amount of salt available in the body to be excreted. Since the salts of the urine, especially sodium chlorid, are increased with diuretics[9] and as sodium chlorid is a salt essential for life, the body takes necessary steps to prevent abnormal depletion of its concentration from the tissues.[9] Recently attention has been brought to the necessity of using an adequate diet ash in the treatment of edema of congestive heart failure.[11] For these reasons no restrictions were placed on the salt intake other than it should be constant from day to day.

Fluid was restricted to 1200 cc. daily. Patients were weighed at the same time each day on a scale which was accurate to 2 ounces and which was brought to the side of the bed. Those too sick to be weighed were not included in this report.

In the early stages of the study, urine output was measured but it soon became evident that it was more accurate to follow the daily weight curve because it fluctuated very much less during the control period. It is important to know the degree of edema present, as there is a definite relationship between the amount of fluid retained by the body and the subsequent diuresis. This point is well illustrated in Figure 1. The urinary output is not an indication of the amount of fluid that can be mobilized in the body for diuresis. The range between the weight before and after diuresis and the level attained when the patient is edema-free is the best indicator for the effectiveness of a diuretic that is available at the present time. Of course it must be understood that loss in weight due to factors other than loss of edema must be controlled. For this reason those patients who could not be controlled as to diet, use of cathartics, vomiting, or any other factor which would influence body weight other than edema of congestive heart failure were excluded from this study.

Twenty patients were studied under controlled conditions. When the weight was constant or increasing after a control period, the

patient was given the diuretic. In those receiving digitalis the diuretic was not given until the patient was completely digitalized and the weight constant on a maintenance dosage. In all cases frequent urine specimens preceding and following each injection were examined especially for red blood cells. The intravenous route was used except in three instances when the drug was given intramuscularly.

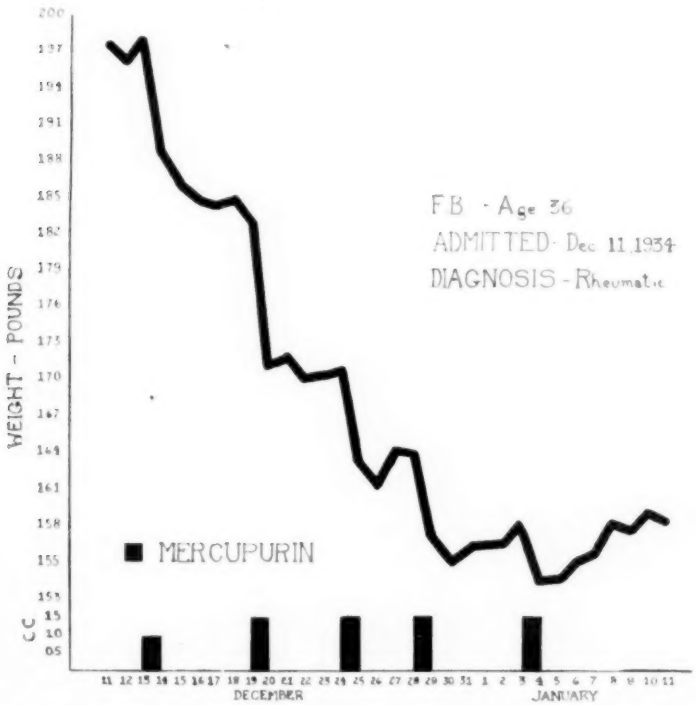


FIG. 1.—Effect of initial body weight upon the diuresis produced by the injection of mercupurin (Case 4, Table 1).

In Table 1 are shown the results of the administration of mercupurin in 10 patients. In every instance a significant weight loss occurred. Diuresis usually began within 4 hours and lasted more than 1 day. In 2 cases it appeared to initiate a diuresis which lasted as long as 4 days. Diuresis was considered complete when the patient stopped losing weight. The greater the amount of edema (as indicated by the patient's weight) the greater the weight loss. In 2 cases, 3 and 5, to whom ammonium chlorid was given, an increased diuresis was obtained even though the patients were on a lower initial weight level. This is in agreement with observations of a number of investigators with other mercurial diuretics. In

no case was there any evidence of a toxic action on the kidney. It is evident from a study of these 10 cases that mercupurin is an efficient and safe diuretic.

TABLE 1.—SHOWING THE DIURETIC EFFICIENCY OF MERCUPURIN (M).

Case No.	Case.	Diuretic cc.	Date.	Amm. chlorid, gm.	Initial wt.	Wt. first day.	Loss first day.	Max. loss.	Days required for wt. loss.
1	J. W.	M.—2.0	8/30	..	150½	138½	12	12	1
		M.—1.0	9/7	..	143	139	4	4	1
2	C. W.	M.—2.0	8/28	..	106	98	8	18	2
3	G. D.	M.—2.0	8/28	..	180½	174½	6	6	1
		M.—2.0	9/1	..	175	170½	4½	7	3
		M.—2.0	9/5	..	169	167½	1½	2½	3
		M.—2.0	9/14	5.4	166½	151½	15	17½	2
		M.—2.0	9/18	5.4	155	145	10	10	1
4	F. B.	M.—1.0	12/13	..	198	189	9	14	4
		M.—1.5	12/19	..	183	171	12	13	2
		M.—1.5	12/24	..	170½	163	7½	9½	2
		M.—1.5	12/28	..	164	157	7	9	2
		M.—1.5	1/3	..	158	153½	4½	4½	1
5	B. J.	M.—1.0	12/15	..	144	141	3	8	4
		M.—2.0	12/18	..	136	135	1	6	3
		M.—2.0	12/22	5.4	131	128	3	6	4
		M.—2.0	12/27	5.4	127	120½	6½	10	4
		M.—2.0	1/3	5.4	120	112½	7½	10½	4
6	N. S.	M.—2.0	1/5	..	123	118	5	5	1
7	W. M.	M.—2.0	1/2	..	209¾	204	5¾	7	2
		M.—2.0	1/5	..	203¾	199	4¾	8	2
8	B. J.	M.—2.0	1/31	..	164	157	7	10	2
9	H. R.	M.—2.0	2/6	..	96½	93	3½	4½	2
10	F. K.	M.—1.0	1/15	..	184	179	5	6½	2
		M.—2.0	2/6	..	166½	164	2½	2½	1

Our next step was to compare mercupurin with a mercurial diuretic having about the same mercury content per injection dose but not containing theophyllin. Salyrgan was found to meet these requirements and had the added advantage of being used extensively. In comparing the efficiency of two diuretics in man difficulties are encountered which make it hard to evaluate the results obtained. Variables are present which can be controlled only in part or not at all. The beneficial effect of diuretics seems to wear off to a variable degree in certain cases after being given over a long period.[3d, 12] They are often less effective when given close together even though the dosage be increased.[3d] On the other

hand, certain patients show an increasing response to mercurials, so that a progressively greater diuresis results. In addition, if the different diuretics are given alternately, we may have the possible delayed effect of the one given earlier. Nevertheless, in spite of these variables, if the results are all in the same direction one would be justified in attaching some significance to them.

Salyrgan is dispensed in a 10% solution containing 39.6% mercury by weight (1 cc. contains 0.0396 gm. Hg). Mercupurin is dispensed in a 13.5% solution containing 29.1% mercury by weight (1 cc. contains 0.0393 gm. Hg). Thus 1 cc. of each preparation contains approximately equivalent amounts of mercury. Each diuretic was administered, using the mercury content as the basis for dosage (except in the first 4 cases where a slightly higher dosage of salyrgan was used).

The diuretics were given alternately, allowing as nearly as possible the patient's weight to return to the initial level before the second drug was given. This was done so that approximately the same amount of retained edema was present in the body before each diuretic was given. As we have just shown, such a control is extremely important because the extent of the diuresis depends in a large part on the amount of edema present. Such a procedure entailed no hardship on the part of the patient because the patient was ready for the second diuretic at about the time it would ordinarily have been given. The cases selected for this study were those who regained weight rapidly. It is probably for this reason that the diuresis did not continue as a rule for more than 1 day, contrary to the group shown previously. In Case 12 (Table 2) the edema was so marked and the clinical condition so poor that it was not desirable to follow this rule quite so rigidly. In Case 18 (Table 3) a series of injections of salyrgan were followed by a series of mercupurin.

The results are shown in Tables 2 and 3. Of the 9 cases tabulated, in 6 mercupurin produced a greater loss of weight than salyrgan, in 2, Cases 12 and 14, the results were equivocal, and in no case did salyrgan produce a greater diuresis than mercupurin. It will be noted that mercupurin was given at times where the initial weight was below that when salyrgan was given and yet the diuresis was the same or even better. With Case 18 (Table 3) mercupurin not only produced a greater loss of weight but the interval between injections could be lengthened and still maintain the patient on a lower average weight level than when he was on salyrgan (Fig. 2).

In order to study more intimately the diuresis of the two drugs the following method was used: The patient was put under practically basal conditions. He was always allowed to regain his initial weight level before the comparison was made, otherwise the results would not be valid. Breakfast, which was essentially the same for every day the observations were made, contained very little

fluid (less than 250 cc.) and was given at 7 A.M. At 9 A.M. the patient voided and the urine was discarded. He then voided every ½ hour for 8½ hours. At 10 A.M. the diuretic was given intravenously. No fluid or food was administered during the period of observation. In the 4 cases in which this was done, it was found that the peak of the diuretic effect was between the 4th and 5th hours with both drugs, and in every case mercupurin reached a higher level and produced a greater total diuresis (Fig. 3).

TABLE 2.—COMPARISON OF MERCUPURIN (M) AND SALYRGAN (S) WHEN GIVEN ALTERNATELY.

Case No.	Case.	Diuretic cc.	Date.	Amm. chlorid, gm.	Initial wt.	Wt. first day.	Loss first day.	Max. loss.	Days required for wt. loss.
11	S. R.	M.—2.0	10/23	..	146	135	11	11	1
		S.—2.2	10/31	..	143½	136½	7	7	1
		M.—2.0	11/7	..	141	132½	8½	8½	1
		S.—2.0	11/16	..	140	133	7	7	1
		M.—2.0	11/22	..	141	131	10	10	1
		S.—2.0	11/28	..	137¾	129	8¾	8¾	1
		M.—2.0	12/4	..	139	128½	10½	10½	1
		M.—1.0	12/15	2.4	138	125	13	13	1
		S.—1.0	12/27	2.4	134	129½	4½	4½	1
12	J. K.	M.—0.9	9/3	..	134	133	1	1	1
		S.—1.0	10/18	..	131¾	130¼	1½	1½	1
		M.—0.9	10/29	..	125	119¼	5¾	5¾	1
		S.—1.0	11/7	..	123¾	120¼	3½	3½	1
		S.—2.0	11/14	..	126	117¾	8¼	8¼	1
		M.—2.0	11/21	..	120	112	8	8	1
13	S. K.	M.—0.9	10/31	..	199	195½	3½	3½	1
		S.—1.0	11/3	..	197¼	198	0	0	0
		M.—1.8	11/7	..	200½	191	9¼	9¼	1
		S.—2.0	11/12	..	195	192½	2½	2½	1
		M.—2.0	11/15	..	191	183½	7½	7½	1
		M.—2.0	11/20	1.8	183½	178	5½	5½	1
14	E. D.	S.—2.2	11/6	..	147	139	7½	7½	1
		M.—2.0	11/13	..	143½	135	8½	8½	1
15	J. B.	S.—2.0	12/18	..	154	154½	0	0	0
		M.—2.0	12/29	..	151	142	9	9	1
		S.—2.0	1/4	..	150	147½	2½	2½	1
16	H. G.	M.—2.0	12/29	..	154	144	10	10	2
		S.—2.0	1/8	..	148½	141	7½	8½	2
		M.—2.0	1/26	..	143	133	10	10	1
17	F. G.	M.—1.0	1/15	..	146	146	0	0	0
		M.—2.0	1/18	..	146	146½	0	0	0
		S.—2.0	1/21	..	158	159	0	0	0
		M.—2.0	1/25	5.4	158	158½	0	0	0

Although these experiments suggested that the presence of theophyllin in a mercurial diuretic would enhance somewhat the

effectiveness of the diuretic, still the experiment was not ideal. Although salyrgan and mercupurin contain approximately the same amount of mercury per dose, still the organic portion of the molecule differs considerably. Therefore, it is possible that this variation in chemical structure rather than the presence of theophyllin might be responsible for the difference in diuretic effectiveness. For that reason a quantity of the theophyllin-free mercurial salt of mercupurin was obtained and put into solution so that the mercury content per dose would be the same as that of mercupurin. Four cases were studied and results are given in Table 4.

TABLE 3.—SUBSTITUTION OF MERCUPURIN (M) FOR SALYRGAN (S) AND VICE VERSA.

Case No.	Case	Diuretic, cc.	Date	Amm. chlorid, gm.	Initial wt.	Wt. first day.	Loss first day.	Max. loss.	Days required for wt. loss.
18 . . .	E. B.	S.—1.0	11/18	..	189	192½	0	0	0
		S.—2.0	11/22	..	190½	184	6½	6½	1
		S.—2.0	11/24	3.6	184	180	4	4	1
		S.—2.0	11/27	..	186	182	4	4	1
		S.—2.0	11/30	..	185	180	5	5	1
		M.—2.0*	12/2	..	182½	180	2½	4	2
		M.—2.0	12/6	..	183	176	7	7	1
		M.—2.0	12/11	..	182	177	5	5	1
		M.—2.0	12/15	..	181½	176	5½	5½	1
		M.—2.0	12/19	..	182½	176	6½	6½	1
		M.—2.0	12/24	..	185	177	8	8	1
		M.—2.0	12/28	..	184	176	8	8	1
19 . . .	F. S.	M.—2.0	2/27	..	118½	114	4½	4½	1
		M.—2.0	3/9	..	118	113	5	5	1
		M.—2.0	3/20	..	117½	113	4½	4½	1
		S.—2.0	4/4	..	118½	116	2½	2½	1
		S.—2.0	4/16	..	119½	117½	2	2	1

* Intramuscular injection.

In 2 cases (Nos. 15 and 20) a greater weight loss occurred with mercupurin than with the theophyllin-free salt. In the 2 others, Cases 18 and 19, the weight loss was about the same for each. This may be due to the fact that the small amount of edema initially present in these 2 patients needed only a small dose of a diuretic to bring the weight down to a basal level, and that the doses given here were therefore in excess of that required. In order to study the difference more closely in these 2 cases, half-hour observations of urinary output, as described above for the comparison of salyrgan and mercupurin, were done. In both cases there was a greater diuresis produced by mercupurin than its salt free of theophyllin. A comparison was also made with salyrgan and it was found that salyrgan and the mercurial salt free of theophyllin gave practically the same results (Fig. 4). These experiments further support the view that it is the presence of theophyllin in the mercupurin which accounts for the greater diuresis.

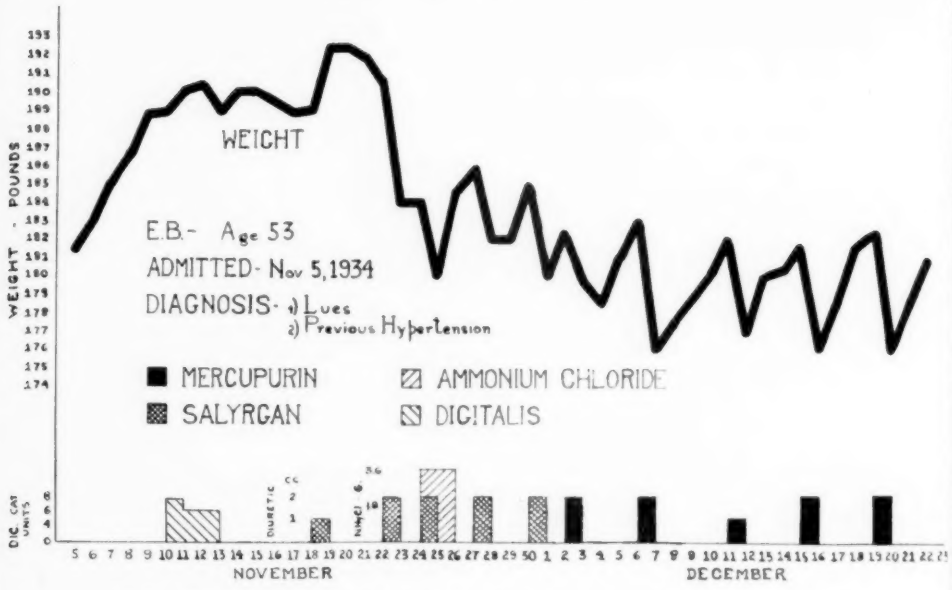


FIG. 2.—Showing greater loss of weight and maintenance on a lower average weight level when mercupurin was substituted for salyrgan (Case 18, Table 3).

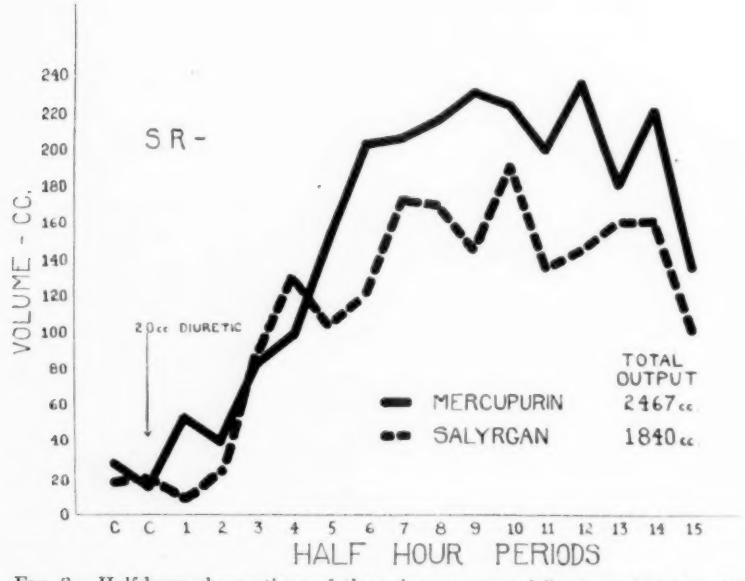


FIG. 3.—Half-hour observations of the urinary output following administration of mercupurin and salyrgan. Patient was allowed to regain initial weight before either diuretic was given (Case 11).

TABLE 4. SHOWING RÔLE PLAYED BY THEOPHYLLIN FRACTION OF MERCUPURIN BY COMPARING MERCUPURIN (M) WITH THE MERCURIAL SALT CONTAINED IN MERCUPURIN FREE OF THEOPHYLLIN (M–T).

Case No.	Case.	Diuretic, cc.	Date.	Amm. chlorid, gm.	Initial wt.	Wt. first day.	Loss first day.	Max. loss.	Days required for wt. loss.
15	J. B.	M.—2.0	12/29	..	151	142	9	9	1
		M-T—2.0	1/15	..	145½	140	5½	5½	1
		M.—2.0	1/21	..	142	138	4	4	1
		M.—2.0	1/24	..	139	135½	4½	4½	1
		M.—2.0	2/2	3.6	135	130	5	6	2
		M.—2.0	2/5	3.6	129½	121	8½	8½	1
		M.—2.0	2/11	3.6	125	118	7	7	1
		M-T—2.0	2/21	3.6	122½	120½	2	2	1
		M.—2.0	2/26	3.6	126¾	121	5¾	5¾	1
		M-T—2.0	2/28	3.6	125½	121¾	3¾	3¾	1
		M.—2.0	3/5	3.6	128	124	4	4	1
		M-T—2.0	3/7	3.6	127½	123	4½	4½	1
		M.—2.0	3/12	3.6	129	121	8	8	1
18	E. B.	M.—2.0	12/28	..	184	176	8	8	1
		M-T—2.0	1/22	..	184	177	7	7	1
20	P. S.	M.—2.0	2/4	..	172½	166	6½	6½	1
		M.—2.0	2/9	..	163	161	2	8	3
		M-T—2.0	2/14	..	156	156	0	0	0
		M-T—2.0	2/19	5.4	150¼	149	1¼	5½	3
		M.—2.0	2/22	5.4	145	142	3	8½	2
19	F. S.	M.—2.0	2/27	..	118½	114	4½	4½	1
		M-T—2.0	3/5	..	116½	113	3½	3½	1
		M.—2.0	3/9	..	118	113	5	5	1
		M-T—2.0	3/14	..	117½	113	4½	4½	1
		M.—2.0	3/20	..	117½	113	4½	4½	1
		M-T—2.0	3/28	..	117½	113	4½	4½	1

In no case was a slough or venous thrombosis produced with 94 intravenous injections of mercupurin, but out of 27 intravenous injections of salyrgan 4 cases developed a thrombosis or slough. The local reactions of both these drugs and the part played by theophyllin will be discussed fully in a subsequent paper.[13]

Although frequent and careful microscopic urine examinations were made throughout, no evidence of damage to the kidney was noted in any case with any of the drugs used. Even in the patient having glomerulonephritis (Case 16), where a mercurial diuretic had to be given because nothing else was effective, no evidence of increased kidney damage due to the mercurials could be detected from a study of the urinary sediment.

Discussion. Organic preparations of mercury in a non-ionizable form have replaced the use of calomel in the treatment of edema. It has been suggested by v. Issekutz and v. Vegh,[4] and later by Fourneau and Melville,[14] that the chemical structure of the various

preparations is an important factor in determining diuretic efficiency and toxicity. Thus, the latter conclude that "mercurial toxicity is not in direct relation to either the quantity *per se* of mercury injected or to the general chemical reactivity of the substance as shown by the action of certain chemical reagents, but rather dependent primarily upon the direct chemical linkage of the metal," while "structural changes in chemical constitution might lead to variation in diuretic activity." It will be recalled that the theophyllin-free mercurial salt of mercupurin differs in its structural formula from that of salyrgan and theoretically should therefore differ in its toxicity and diuretic effectiveness. The evidence submitted by v. Issekutz and v. Vegh[4] indicates that salyrgan is more toxic than the theophyllin-free mercurial salt of mercupurin, but neither they, in their animal experiments, nor we, in our work in man, were able to detect any measurable differences in the diuretic effectiveness of the two drugs.

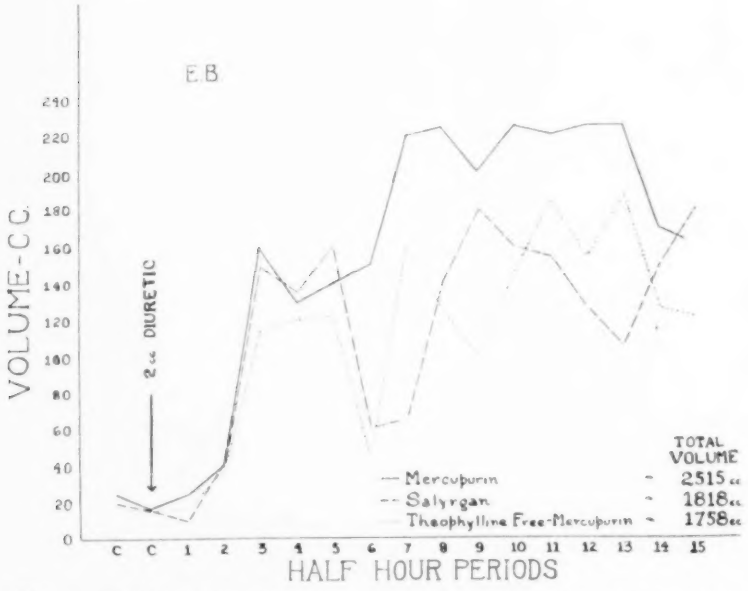


FIG. 4.—Half-hour observations comparing mercupurin, salyrgan and the theophyllin-free mercurial salt contained in mercupurin. Patient was allowed to regain initial weight before each diuretic was given (Case 18).

The question of the mechanism of the diuresis resulting with xanthin and mercurial preparations, although still open to dispute, was markedly clarified with the use of Rehberg's[15] method for measuring glomerular filtration and tubular reabsorption. Evidence at the moment indicates that both the xanthins and mercurials have their action directly upon the kidney, the former increasing

glomerular filtration and the latter decreasing tubular reabsorption. The literature on this subject has been recently reviewed by Schmitz[16a] and Binger and Keith.[16b] If the mechanism of diuresis is such that both types of diuretics have different sites of action in the kidney, it is evident then that upon purely theoretical grounds a combination of both would possess possible advantages. The results of v. Issekutz and v. Vegh,[4] who were the first to use a combination of both diuretics, have already been discussed. Recently Herrman[17] and his coworkers have likewise found clinically that, when the diuretics were given together or alternately, a better clinical result was obtained.

From our results it is also seen that theophyllin plays a part when combined with a mercurial salt in the removal of edema fluid. This is in accord with the results of Crawford and McDaniel[7] in their comparison of mercupurin and salyrgan and the experimental work of Fulton and Bryan.[8]

Conclusions. 1. Mercupurin is an effective and safe diuretic.

2. The diuretic effect of mercupurin is greater than that of a mercurial diuretic not containing theophyllin.

3. The superiority of mercupurin is chiefly if not entirely due to the presence of theophyllin.

4. No local reaction from intravenous administration of mercupurin was noted in 94 injections.

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ON THE DIFFERENTIATION OF COLORED CEREBROSPINAL FLUIDS.

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In this communication we wish to report upon studies of colored spinal fluids; to try to define more exactly their mode of production and to suggest the routine use of the benzidin test in their etiologic differentiation.

Froin,[1] in 1903, first directed attention to the "syndrome de coagulation massive et de xanthochromia" which now bears his name. Nonne,[2] some 5 years later, described a marked increase in protein, but with no pleocytosis or xanthochromia in 3 cases of cord tumor. Hanes,[3] in 1916, correlated the findings of Froin and Nonne by pointing out that the Nonne syndrome represents the earliest spinal fluid change in cord compression, whereas the Froin syndrome is the result of long-standing cord compression which produces a cul-de-sac distal or caudad to the lesion. "Any pathologic alteration of the vertebræ, dura mater or pia arachnoid which leads to partial or complete obliteration of the pia arachnoid space and the formation of a cul-de-sac is capable of producing the syndrome of xanthochromia with excess protein and massive coagulation. If the pathologic change is associated with inflammation of

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the meninges there will be a leukocytosis of the fluid, but when the compression is due to non-inflammatory growths no pleocytosis is present." Ayer,[4] in 1919, produced xanthochromia with an increase of protein without pleocytosis in cats by the epidural injection of molten paraffin.

Colored spinal fluids (1) may be produced by hemorrhage into the subarachnoid space, (2) by spinal cord compression, (3) by severe inflammatory reactions, (4) by carotinemia and (5) are found in the xanthochromia of the newborn. Obviously it would be of great aid if some simple test could be used which would separate yellow fluids due to compression on the one hand, from tingeing of the fluid from hemoglobin or its derivatives. During the past 3 years the benzidin test as modified by Schlessinger and Holst[5] has been used routinely in the medical clinic of Duke Hospital upon all spinal fluids. Devine and Robinson, of this clinic, by a carefully controlled series of studies (unpublished) were able to show that the benzidin test for hemoglobin in the cerebrospinal fluid is positive in dilutions up to 1 in 50,000 (or about 100 red cells per cc.), but is negative in dilutions of 1 in 100,000 (or 50 cells per cc.). In a series of 100 fluids obtained from routine punctures they found that 12 (8%) gave a positive benzidin test, and all of these contained more than 100 cells per cc. After centrifuging such fluids the supernatant fluid did not give a positive benzidin test.

The conditions are quite otherwise in cerebrospinal fluids discolored by subarachnoid hemorrhage. Here, except in very early bleedings, which cause no confusion, the supernatant fluid after centrifuging gives a strongly positive benzidin reaction. We have been able to follow the cerebrospinal fluid in 1 case of subarachnoid hemorrhage until all tingeing had disappeared, but this perfectly clear untinged fluid still gave a positive benzidin reaction.

The literature contains very few data on the benzidin reaction of the yellow fluids found in the cord compression syndrome. This problem seemed peculiarly suited to experimental study. We have devised the following method by means of which a slowly developing compression of the spinal cord in dogs can be produced. The laminæ of the third and fifth thoracic vertebræ are resected, leaving the fourth lamina in place. If now a small collodion bag filled with a concentrated suspension of gum acacia is placed beneath the fourth lamina extradurally, and the wound closed, the collodion bag slowly distends and compresses the cord. Bags of various sizes were used, containing from 0.25 to 0.5 cc. of gum acacia and compressions of varying severity could thereby be accurately produced. From our 14 protocols we have selected 4 as typical.

Protocols. *Dog 4.*—A collodion sac filled with a solution of acacia was inserted epidurally under the fourth thoracic vertebra. The dog walked for 2 days without motor impairment and then began to manifest increas-

ing spasticity of the lower extremities which amounted to a paraplegia on the 8th day. On this day the cerebrospinal fluid below the block was clear yellow and coagulated on standing, reacted negatively to the benzidin test, gave a 3+ Pandy reaction and contained 8 leukocytes per c.mm., no erythrocytes. The dog was sacrified and autopsied on the 14th day and the fluid at this time was yellow, gave a negative benzidin reaction, a 3+ Pandy, contained 18 leukocytes and no erythrocytes. The cord was found compressed by the collodion bag and the veins of the spinal canal and dura were markedly dilated below the block and slightly dilated for a few centimeters above the block.

Dog 7.—A collodion bag containing a concentrated solution of glucose was inserted epidurally in this case and the dog was unable to walk after operation. Prior to autopsy on the 4th day, however, slight return of function was noted. A lumbar puncture was done about 18 hours after operation and the fluid was clear, colorless, contained 2 leukocytes and gave a negative benzidin and Pandy reaction. On the 4th day the animal was sacrificed and autopsied. The collodion bag was found to have ruptured and the dura was adherent at the level of the block. There was only slight venous engorgement below the block. The cerebrospinal fluid was yellow, contained 10 leukocytes and gave a negative benzidin reaction and a 3+ Pandy.

Dog 8.—One day after operation (collodion and acacia bag) this dog began to show weakness of the hind legs in walking, which progressed to a paraplegia by the 3d day and continued throughout the course of the experiment. On the 3d day the cerebrospinal fluid below the block was removed. It was yellow, gave a negative benzidin reaction, a 3+ Pandy, contained 6 leukocytes and 82 erythrocytes. A lumbar puncture on the 10th was contaminated with blood and it was noted that the last drops did not appear bloody. This fluid contained 18 leukocytes, 576 erythrocytes, gave a strongly positive benzidin reaction and a 3+ Pandy. After centrifuging at high speed, the supernatant fluid was yellow, contained no cells and gave a 3+ Pandy reaction and a negative benzidin. At autopsy on the 10th day the cord was found compressed by the collodion bag and the veins of the spinal canal and dura were markedly engorged below the block and obliterated at the level of the block with a slight engorgement for 2 or 3 cm. above the site of compression.

Dog 2.—This dog began to manifest some weakness of the hind legs on the day after operation (collodion and acacia bag) which progressively became more marked, but he was able to move his legs at the time of his sacrifice on the 3d day. On this day an autopsy was performed and the cerebrospinal fluid below the block was yellow, contained 6 leukocytes, no erythrocytes, gave a negative benzidin reaction and a 3+ Pandy. The cord was found only slightly compressed. The veins at this level, however, were obliterated. They were engorged below the block and were slightly more prominent than normal for a few centimeters above the level of compression.

Dog 14.—In this case a tape, about 1 cm. in width, was tied snugly about the cord epidurally, and immediately after the animal regained consciousness a paraplegia was evident. The animal was left with this paraplegia in extension for 5 days and then autopsied. The cerebrospinal fluid below the block was yellow, clear and contained 4 leukocytes, no erythrocytes, gave a 3+ Pandy and a negative benzidin response. The tape constricted the spinal cord to a rather marked degree and also pressed against the anterior longitudinal veins of the canal and obliterated them at this level; but they were markedly engorged below the block and for a few centimeters above the block were more than normally prominent. The veins of the dura below the block were engorged.

In every case a routine cisterna puncture was done at autopsy and the cerebrospinal fluid removed was uniformly normal.

Comment. The severity of the symptoms of cord compression was directly proportional to the size attained by the collodion bag and to the duration of the compression. As a rule, the animal was able to walk quite normally for 2 or 3 days following the operation, but a progressive weakness of the legs then developed which, on the fourth day, culminated in paraplegia in extension.

Cerebrospinal fluids removed by lumbar puncture within the first 24 hours were quite normal, and fluids removed from the cisterna magna were always normal regardless of the severity or duration of the cord compression. After the first day the changes in the cerebrospinal fluid below the block were remarkably constant. There was at first a marked increase in protein, which in prolonged blocks resulted in spontaneous massive coagulation of the fluid removed. Such fluids showed a canary yellow color, but no pleocytosis. *The benzidin reaction was uniformly negative on all fluids.* We feel that we can state positively that the cerebrospinal fluid in the pure syndrome of spinal cord compression does not give a benzidin reaction.

At *autopsy* identical findings were observed in all animals, consisting of compression of the cord by the distended bag with obliteration of the subarachnoid space and the formation of a cul-de-sac below the block. For about 3 cm. above the area of compression and 7 cm. below the venules of the leptomeninges were greatly engorged. Lying extradurally there are 2 longitudinal veins in the anterior portion of the spinal canal which anastomose with radicles from each segment of the cord, and with veins which run along the vertebral column outside the canal. These veins were found to be compressed at the region of the block and engorged for a few centimeters above and below the block, in which latter position they were especially prominent, being about 3 times their normal size. Microscopic studies of the spinal cords showed no inflammatory changes.

Discussion. The possibility of distinguishing between xanthochromia, whether due to hemorrhage, to inflammation or to cord compression, has been denied by certain observers.[6] Hanes,[3] in 1916, in his discussion of a case of spinal block with yellow fluid of high-protein content, pointed out that the benzidin reaction was negative and that the veins below the block were greatly engorged. He suggested that such spinal fluid findings were due purely to venous stasis with transudation. Our results support this conclusion. We believe that the benzidin reaction offers a simple and positive means of differentiation between spinal block without inflammation on the one hand, and hemorrhagic xanthochromia on the other. The use of the designation "erythrochromia" for tingeing of the fluid due to hemorrhage or inflammatory diapedesis,

and the restriction of the term xanthochromia to the yellow fluid, rich in protein, of the pure Nonne-Froin pressure syndrome, seems justifiable in the light of the experiments here reported.

Summary. 1. The benzidin reaction is positive in cerebrospinal fluid containing a hemoglobin dilution of 1 to 50,000 (100 erythrocytes per c.mm.), but not to a dilution of 1 in 100,000 (50 erythrocytes per c.mm.).

2. The benzidin reaction on the supernatant fluid after centrifuging at high speed is of value in differentiating hemorrhage into the cerebrospinal fluid at the time of puncture from subarachnoid hemorrhage.

3. An extramedullary tumor compressing the spinal cord in its growth has been reproduced experimentally in dogs with a resulting Nonne-Froin syndrome in the cerebrospinal fluid below the level of the compression.

4. The yellow spinal fluid of cord compression gives a negative benzidin reaction.

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EARLY PULMONARY TUBERCULOSIS AND ITS DIAGNOSIS.

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The Problem. Though the importance of early diagnosis has been heralded for years, pulmonary tuberculosis is usually not discovered in its minimal stage. Upward of 80% of patients on admission to sanatoria are either in a moderately or far advanced stage of the disease. Treatment then usually requires a long period of time, often presents many difficulties, and the prognosis is only mildly encouraging, viewed after 5, 10 and 15 years. Whitney[1] reports that of 37,665 cases of frank pulmonary tuberculosis reported by 274 institutions (U. S.) in 1931, 5939 (16%) were admitted in the minimal stage, 11,057 (30%) in the moderately advanced and

19,669 (54%) in the far advanced stage. Compared to the earlier figures (1926) of Drolet,[2] the percentage admitted in the minimal stage, 16%, is the same, but in 1931 the percentage of far advanced is higher, being 54% as compared with 50% in 1926.

Watt[3] of England, successfully tracing 603 of 677 cases 5 years after their discharge in 1925 from the King George V Sanatorium, found that of 149 early cases, 21.5% were dead, 64.5% alive and fit for work, and 14% alive but not fit for work. Of 385 moderately advanced cases, 63.5% were dead, 24.5% alive and fit for work, and 12% alive and not fit for work. Of 69 far advanced cases, 91% were dead, 4.5% alive and fit for work, and 4.5% alive but not fit for work. Today with better methods of treatment the mortality rate would undoubtedly be less but still substantial. The figures of the early cases after 5 years offer a striking contrast to those of the moderately and far advanced cases. The report of the Trudeau Sanatorium[4] also emphasizes the necessity of early diagnosis. After 15 years only 10% of the minimal are dead, compared to 27% of the moderately advanced and 72% of the far advanced cases.

TABLE 1.—CONDITION OF DISCHARGED PATIENTS (TRUDEAU SANATORIUM) 5, 10 AND 15 YEARS AFTER DISCHARGE.

Classification on admission.	Dead of tbc. first 5 yrs.		Dead of tbc. second 5 yrs.		Dead of tbc. third 5 yrs.	
	No.	%	No.	%	No.	%
Minimal, 627 (20%)	21	3.3	24	3.1	17	3.6
					Total, 15 yrs., 62	10.0
Moderately advanced, 2033 (65%)	242	11.9	262	10.0	131	5.5
					Total, 15 yrs., 635	27.4
Far advanced, 449 (14%) . .	196	43.6	83	18.0	104	10.6
					Total, 15 yrs., 383	72.2

TABLE 2.—PROGNOSIS OF 37,665 CASES OF PULMONARY TUBERCULOSIS ADMITTED TO 247 U. S. INSTITUTIONS 1931, ACCORDING TO THE TRUDEAU SANATORIUM EXPERIENCE.

Classification on admission.	Dead of tbc. first 5 yrs.		Dead of tbc. second 5 yrs.		Dead of tbc. third 5 yrs.	
	No.	%	No.	%	No.	%
Minimal, 5939 (16%)	196	3.3	184	3.1	214	3.6
					Total, 15 yrs., 594	10.0
Moderately advanced, 11,057 (30%)	1,345	11.9	1,130	10.0	621	5.5
					Total, 15 yrs., 3,096	27.4
Far advanced, 19,669 (54%) . .	8,577	43.6	3,540	18.0	2,084	10.6
					Total, 15 yrs., 14,201	72.2

The experience of patients in the minimal, moderately advanced and far advanced groups 5, 10 and 15 years after discharge from the Trudeau Sanatorium is shown in Table 1. Table 2 represents

the prognosis of 37,665 cases admitted to 274 United States Sanatoria in 1931 based on the Trudeau experience. Why only 16% are admitted in the minimal and 54% in the far advanced stage with prognosis bad, requires an explanation. The explanation, as will be shown, lies in the fact that pulmonary tuberculosis in its minimal stage is without symptoms sufficient to bring the patient to the physician, and without physical signs in most instances by which a diagnosis could be made if the patient did present himself. The discovery of early tuberculosis is dependent on the roentgenogram and fluoroscopic examination of those infected as determined by the properly administered Mantoux tuberculin test.

Gaspard-Laurent Bayle rightfully wrote over a century ago: "Many physicians seem to have confused phthisis with its characteristic signs, and as emaciation and the hectic fever are two of the ordinary symptoms of phthisis, it seems absurd to them to consider an individual as suffering from phthisis, in whom no fever nor emaciation can be discovered. This manner of considering phthisis is just as ridiculous as that of the naturalist, who seeing a young oak tree, would refuse absolutely to give it this name because it did not yet show all its generic and specific characteristics. Moreover, the oak which has just grown out of the ground, although it is a very feeble plant, is none the less a tree whose trunk will acquire a great deal of strength. It is the same with phthisis: in the beginning it seems scarcely a slight indisposition: in its last stages it strikes down the strongest man, it devours, consumes and reduces to a skeleton those whose plumpness, freshness and health appeared unalterable. Nevertheless, it would be unreasonable to refuse to admit that it is always the same disease, and to maintain this opinion and insist that in its earliest stages it did not show all the symptoms which characterise it today.

". . . But today our knowledge is too advanced to fail to diagnose phthisis in the first stages of this disease, although frequently there has been no perceptible loss of weight and not the slightest trace of pus in the expectoration. . . . It would be hardly reasonable to wish to wait before diagnosing pulmonary phthisis until it had arrived at its last stage which is the time when its pathognomonic symptoms are well marked. Is it not then undebatable that a physician should seek to know a disease from its beginning, through all the stages of its development, and in all its forms, just as the gardner distinguishes the plants which he cultivates through all the stages of their growth, and as an entomologist recognizes an insect in all its metamorphoses?"

Today we are learning more of the disease in its early stage, and have already found the important fact that many times it produces less than the slight indisposition spoken of by Bayle—that in most instances it occurs without producing symptoms or physical signs.

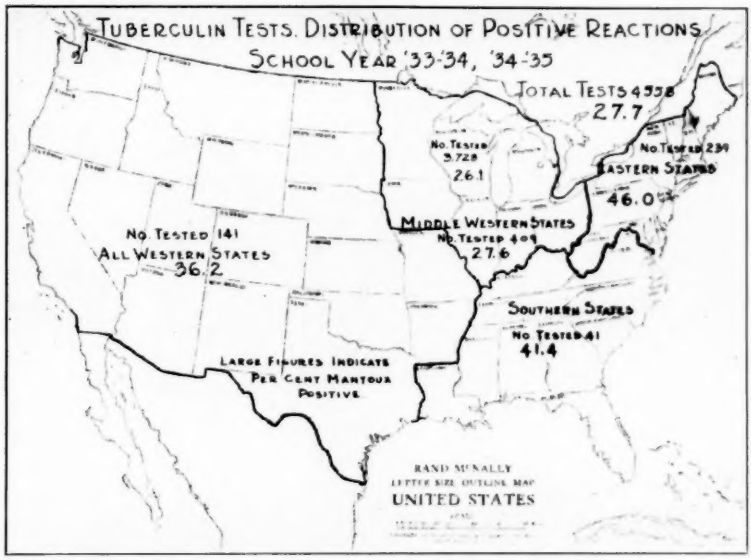


FIG. 1.—Geographical distribution of infection.

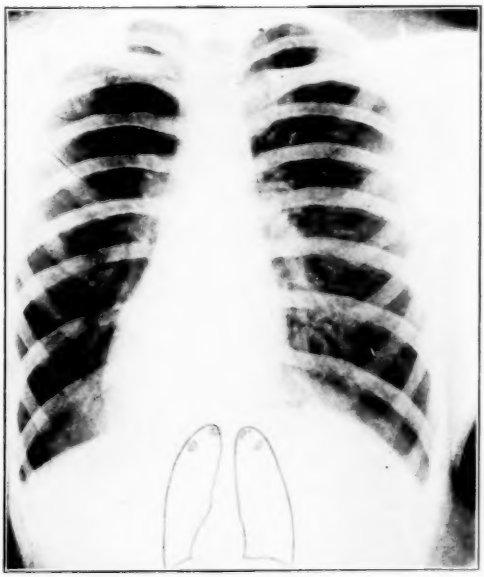


FIG. 3.—Patient T. H., 1-23-35. Early infiltration. No symptoms or physical signs. Laboratory studies negative.

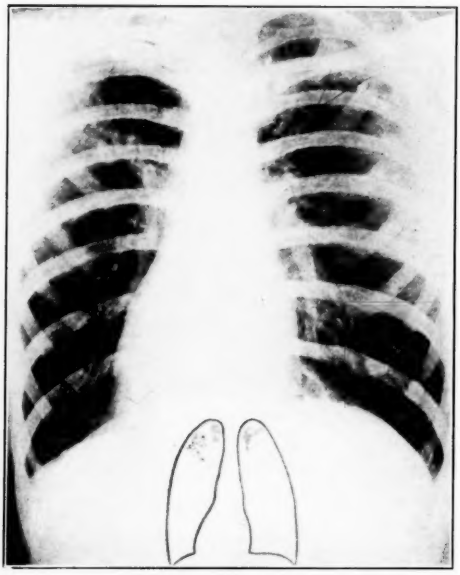


FIG. 4.—Patient T. H., 6-1-35. Spread of lesions without symptoms or physical signs. Patient has gained 8 pounds in weight. Laboratory studies indicative of spread.

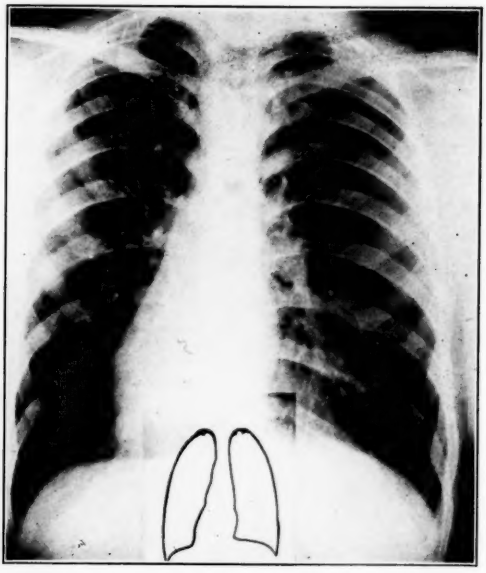


FIG. 6.—Case 80551, 2-10-35. Small infiltration at extreme apices. Negative studies.

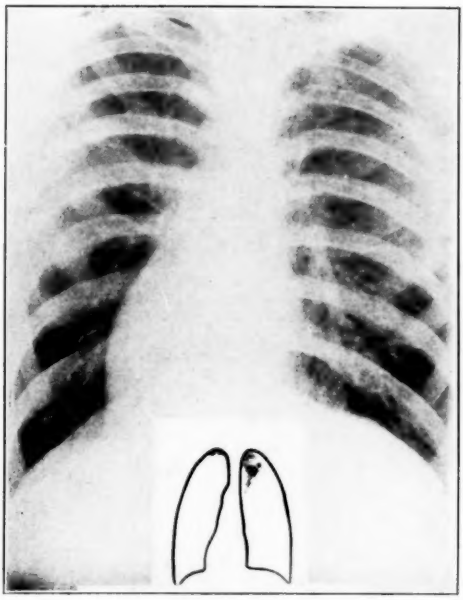


FIG. 7.—Case 80551. Lesion 11 months later; discovered by fluoroscopic examination. Weight gain. 11 pounds. Leucocytosis. No other positive studies.

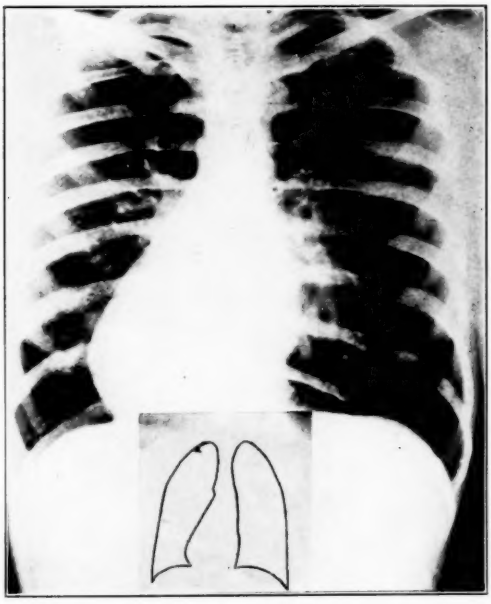


FIG. 9.—Case 73344. Small infiltration discovered by fluoroscopic examination.

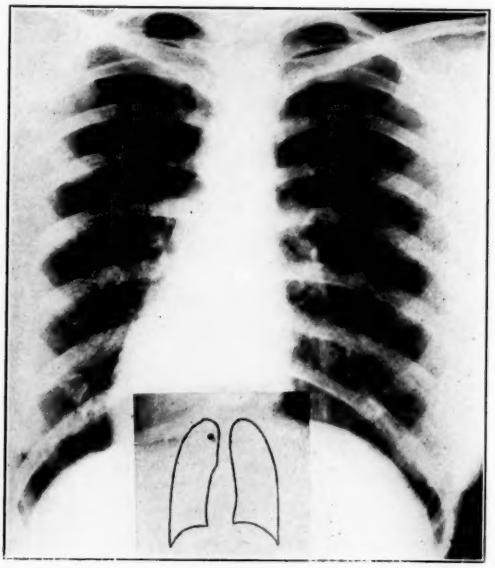


FIG. 10.—Case 69634; 5-20-35. Infiltration partially obscured by bony framework, clearly visible by fluoroscopic study by changing individual's position.

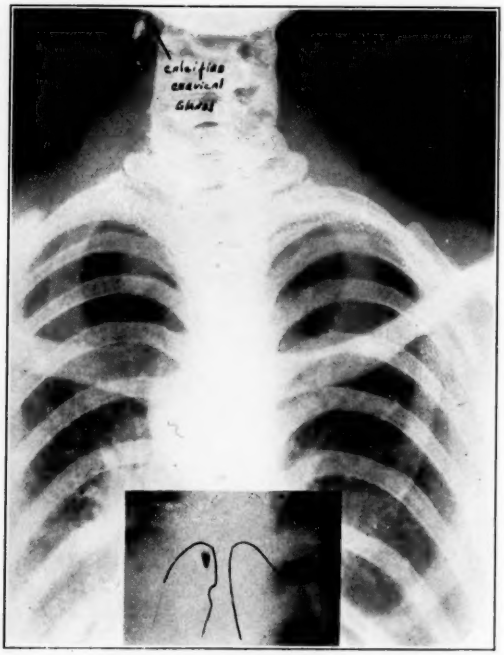


FIG. 11.—Case 69634; 5-22-35. Same infiltration with change of position. Note calcified cervical nodes. Tonsils tuberculous. Lesions in lungs, 12-10-35, has spread to six clavicular regions without development of symptoms or physical signs.

The Program. A case-finding study was instituted in the fall of 1933 on all the newly enrolled students. With the routine physical examination, all students are given the Mantoux test. At the first test either 0.1 mg. of the Saranac Laboratory old tuberculin (O.T.) or 0.00002 mg. of the Purified Protein Derivative (P.P.D.) of Seibert and Long is given. The site of the injection is observed at the end of 48 hours and if no reaction has occurred, the procedure is repeated, using 1 mg. O.T. or 0.005 mg. P.P.D. Those showing positive reactions are further studied by means of the roentgenogram. Infiltrations are thus discovered that require further immediate study which is done in the Student Infirmary. The status of the lesion having been determined, the patient is either advised to withdraw from school for treatment or given instructions to report for examination at regular intervals. Those having suspicious shadows are examined by means of the fluoroscope and Roentgen ray films at intervals of from 4 to 12 weeks, depending upon the degree of suspicion attached to the lesion. Regardless of the fact that the first film may be negative, the tuberculin-positive student receives a fluoroscopic examination every 6 to 12 months while he is attending school. Should the fluoroscopic examination reveal any suspicion of trouble, another roentgenogram is requested. In an individual of heavy proportions, the fluoroscope has its limitations, and is not relied upon to exclude an early infiltration. In those, however, of moderate or light build it makes possible, in our opinion, the discovery of all significant infiltrations to a degree which closely approximates the roentgenogram.

Tuberculin Tests. Of a total of 5316 individuals tested with a dose of at least 1 mg. O.T. or 0.005 mg. P.P.D., 1490 (28%) have shown positive reactions.

The distribution of infection among students from different sections of the country is shown in Figure 1.

To determine the rate of increase of infection, a group of students entering the University in the fall of 1933 and having negative reactions at that time was again tested 18 months later. Of the 485 originally negative students tested, 45 (9.3%) had become infected.

The opportunity was also presented to test a group of 15 sorority girls who had unfortunately lived for 3 months with a senior girl who had entered the university prior to the institution of the program and who subsequently was found to have far advanced tuberculosis. Examination of her sputum showed many tubercle bacilli. Of the 15 tuberculin tested, 11 had formerly been negative. Eight had been tested in the fall of 1933 and 2 in the fall of 1934. One received a test in high school in 1932 which was reported negative. Of the 11 known to have been negative, all (100%) showed a positive reaction in March, 1935. Of the 4 having no previous test, 3 (75%) were positive. The one individual show-

ing a negative test stated that she had lived in the house for only 2 weeks, and this short contact probably explains her escape from infection. Of the 15 tested, 14 (93.3%) showed a positive reaction. Of the 11 known to have been infected, one has developed a progressive lesion (November, 1935) in the left subclavicular region.

Cases Without Symptoms or Physical Signs. Study of the early cases discovered, a few of which are presented, indicates that the progressive pathologic process occurs without the production of symptoms or physical signs. Development of symptom and physical signs indicates in most instances that the disease is no longer in the minimal stage. One individual developed, from a small rather hard appearing right subclavicular infiltration which had shown no change during 11 months observation, a 2.5 cm. by 1.5 cm. cavity between January 22, 1935, and March 4, 1935, a period of 40 days. His only symptom was slight fatigue, and he was already

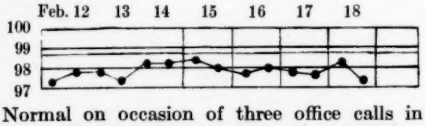
FIG. 2.—CASE NO. 79480. T.H. OCTOBER, 1933.

History: Home, city. Scarlet fever, age 10. Always healthy. Father died of appendicitis; mother living and well; brothers, 1 living and well; sisters, 0. Mantoux, ++.

Symptoms: None.

Physical Examination: Well-developed and nourished, healthy appearing boy, aged 20. Chest examination: essentially negative in October, 1933, January, 1934 and June, 1934. Bl. pr., 114/74, ht., 5′8″, wt., 120, September, 1933. Wt., 130, January, 1934. Wt., 138, June, 1934.

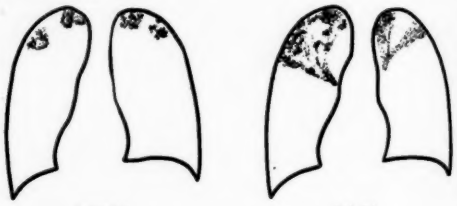
Temperature:



Normal on occasion of three office calls in June. Family physician on a 4-hr. check has never observed a fever, June–July, 1934.

Laboratory: Blood sedimentation index: 3 mm. on January 9, 1934; 4 mm. on March 16, 1934; 12.5 mm. on June 1, 1934. Blood count: leuk., 13,450; polys., 74%; lymph., 26%. No sputum examination. No examination of gastric content.

Roentgenograms:



Treatment: Sanatorium care advised.

Subsequent course: Resting at home. Family physician states, January, 1935, that patient has on no occasion had a fever. No Roentgen ray has been taken to show progress.

April 26, 1935: Roentgenologist reports clearing of infiltrations. Patient continues to be free of symptoms.

in the moderately advanced stage of the disease. Examination of the morning gastric contents of his stomach showed the presence of tubercle bacilli. As concerns symptoms with progressive minimal infiltrations, the individual will occasionally admit slight fatigue. The earliest and most suggestive physical finding, if one be present, is decreased excursion, usually in the subclavicular region, on the affected side.

Case 79480 represents a progressive lesion without the production of symptoms or physical signs. Note the gain in weight of 18

pounds. The blood sedimentation index done on the date of the latest Roentgen ray heralded the spread of the lesion. A more recent report (April, 1935) indicates that the infiltration has shown marked clearing on a regimen of rest at home. On no occasion during his treatment has a fever been found to be present.

FIG. 5.—CASE NO. 80551. J. F. FEBRUARY, 1934.

History: Home, city. Always well. No childhood or other diseases. Mother dead, rheumatic fever; father living and well; brothers, 2 living and well; sisters, 1 living and well. Mantoux, +, September, 1933.

Symptoms: None.

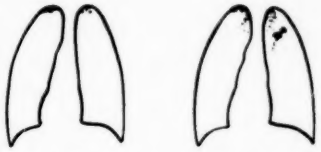
Physical examination: Nothing pertinent. Chest examination: Negative, September, 1933, February, 1934, February, 1935. Ht., 70″; wt., 125, September, 1933; wt., 138, February, 1935.

Temperature: Week of February 27, 1934, normal. Week of February 2, 1935, normal.

Laboratory: Blood sedimentation: 3 mm., February, 1934, and 3 mm., February, 1935. Leukocyte count, 12,700; polys., 73%; lymph., 25%; L.L., 2%. No sputum available for examination. Gastric aspiration not done.

Fluoroscopic examination: January 14, 1935: Feels well; no symptoms referable to chest; half-dollar-sized infiltration in right subclavicular region; stereo of chest requested.

Roentgenograms:



2-10-34 1-14-35 2-21-35

Treatment: Entered sanatorium in February, 1935.

Subsequent course:

FIG. 8.—CASE NO. 79831. A. S. DECEMBER, 1933.

History: Measles, mumps and chickenpox in childhood. Always well. No known tuberculosis contacts. Father living, not well, arthritis; mother living and well; brothers, 0; sisters, 1 living and well. Mantoux, ++; 0.1 mg., September, 1933.

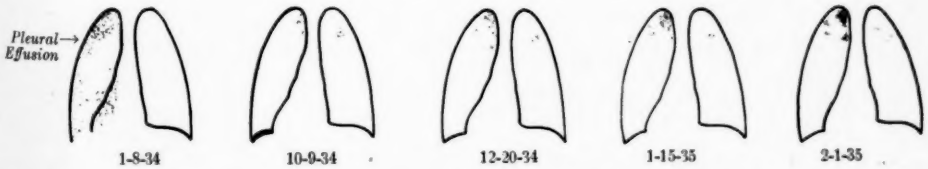
Symptoms: Well, until sudden onset of cough, backache, chest pain and temperature 103° F. Pleurisy with effusion developed for which patient was confined to University infirmary for 6 weeks. Returned home in January, 1934. Continued improvement and patient returned to school in September, 1934.

Physical Examination: October, 1934: Well-developed and nourished girl, aged 19. Chest: left clavicle prominent. Decreased excursion both anteriorly and posteriorly. Impaired resonance left base. No râles.

Temperature: Normal, week of December 22, 1934, and week of January 24, 1935.

Laboratory: Blood sedimentation index: 12 mm., October 13, 1934; 7 mm., December 21, 1934; 25 mm., January 3, 1935; 21 mm., January 11, 1935. Blood count: average count during hospitalization with pleural effusion, 7600 W.B.C., with 70% polys., 25% lymphocytes, 1 to 4% monocytes, 1 to 2% eosinophils. Pleural effusion: 200 cells per c.mm., 97% lymph. and 3% polys. October 8, 1934: 85% Hgb., 5,410,000 R.B.C., 8250 W.B.C., 67% polys., 30% lymph. January 13, 1935: 75% Hgb., 4,700,000 R.B.C., 7400 W.B.C., 75% polys., 24% lymph. Sputum examination: no expectoration. Gastric aspiration not done. Urinalysis negative. Pleural effusion stains. Tuberculosis negative.

Roentgenograms: December 1, 1933: guinea-pig inoculation; pig died, December 22, 1933; no evidence of tuberculosis.



1-8-34 10-9-34 12-20-34 1-15-35 2-1-35

Treatment: Entered sanatorium, February, 1935. Was unhappy. Returned home.

Subsequent course: December 10, 1935. Roentgenograms show marked clearing of infiltrations with bed rest at home.

Case 80551 shows an entirely negative study, and a weight gain of 13 pounds, with a progressive infiltration discovered by fluoroscopic examination.

Case 79831 shows a progressive lesion following pleurisy with effusion. At no time after the original episode of pleurisy with effusion were clinical symptoms present.

Fluoroscopic Examinations. Examination of the lungs by the fluoroscope is economically more practical than the roentgenogram. Where an infiltration or a suspicion of an infiltration is found on the fluoroscopic examination, a film is requested. In individuals of moderate build there is little difficulty in visualizing lesions. Cases 73344 and 69634 show two small infiltrations discovered by this method. Fluoroscopic examination of individuals of moderate or light build has certain advantages over the film. A small lesion on the film is occasionally obscured by the clavicle, which on fluoroscopic examination, because the individual's position is frequently changed, is easily brought into view. The infiltration of Case 69634 was found by fluoroscopic examination, and was thus more easily discerned than on the first roentgenogram taken. The second film was taken during expiration to lower the clavicle and bring the lesion into better view. Study of the excursion of the ribs and diaphragm is not possible with the film. Routine study of the mediastinum in the transverse and oblique views is not economically justified with films. Differentiation between calcified deposits and blood vessels is readily possible on fluoroscopic examination by changing the patient's position.

This work is being done with the regular vertical fluoroscope equipped with the latest type fluoroscopic screen and an exceptionally fine-focus Coolidge tube to give the contrast and detail necessary. The new type "B" Patterson fluoroscopic screen and the XP–3 water-cooled Coolidge tube are used. Five milliamperes are usually required with a kilivoltage ranging from 76 to 85 K.V.P., depending on the size of the patient and the pathologic process present.

TABLE 3.—ROENTGENOLOGIC EXAMINATIONS. CLASSES OF 1937 AND 1938.

Total number positive Mantoux tests using old tuberculin and purified protein derivative, 1440			
Number given roentgenologic examination, 1335. Percentage of positive reactors receiving roentgenograms, 92.7%		Percentage of those receiving roentgenograms.	Percentage of the 5123* students who received the tuberculin test.
Number with no evidence of pulmonary tuberculosis	926	69.4	90.0 (4609)†
Number with first infection type of tuberculosis	333	25.0	6.5
Number with reinfection or adult type of tuberculosis	76	5.6	1.5
Number of positives not receiving roentgenogram, 105	...	...	2.0
	1,335	100.0	100.0
Number with lesions advised to withdrawn from school	21	1.6	0.4

* These figures are arrived at by assuming that all negative reactors would show no tuberculous lesion on Roentgen ray.

† This figure is arrived at by subtracting total number of positives from total tested and adding the number with no Roentgen ray evidence of tuberculosis.

Incidence of Tuberculosis Among Students. Table 3 gives the roentgenogram interpretation of those infected as shown by the positive Mantoux test. Comparing the interpretation of 529 films in September of 1933 with 724 films taken in September of 1934, it is interesting to note the consistency of negative films and the type of lesions found.

	1933, %	1934, %
No evidence of pulmonary tuberculosis	70.7	69.2
First infection tuberculosis	24.2	24.9
Adult tuberculosis	4.9	5.9

Of the 21 withdrawing from school, 15 were advised to leave soon after admission following a short period of observation at the Student Infirmary. Six withdrew the following year because of development or progression of small lesions.

Summary. 1. Pulmonary tuberculosis is seldom discovered in its minimal stage.

2. The pathologic process of minimal pulmonary tuberculosis seldom causes symptoms or physical signs.

3. The diagnosis of minimal tuberculosis is dependent upon periodic Roentgen ray or fluoroscopic examination of the infected as indicated by the Mantoux test.

4. Fluoroscopic examination of the lungs makes possible at a low cost the discovery of significant minimal infiltrations.

5. The methods employed have been efficient in finding pulmonary tuberculosis in its early stages. In no instance of over 4000 individuals being periodically examined has one presented himself because of symptoms of tuberculosis, yet in this group asymptomatic pathologically progressive cases of tuberculosis were discovered.

Conclusions. 1. The eventual institution throughout the country of a program of periodic Roentgen ray or fluoroscopic examinations of all the infected is logical. Consideration of the cost of treatment of tuberculosis, makes a program for early discovery economically justifiable.

2. Would it not appear even more logical to advocate and apply such a case finding program as a public health measure for the general population, rather than limiting it to small groups, and in the end pay the penalty of high morbidity and mortality of late diagnoses? Costs count, and money could more profitably be spent in prevention of symptomatic tuberculosis with its hardships and suffering, than in waiting for patients who are the end-products of the disease and attempting to reclaim them.

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3. Watt, J.: Difficulties in the Early Diagnosis of Pulmonary Tuberculosis, J. State Med. Soc., **42**, 274, 1934.

4. Personal communication and Report of Medical Director, F. H. Heise, Trudeau Sanatorium, Saranac Lake, New York.

BOOK REVIEWS AND NOTICES

THE AUTONOMIC NERVOUS SYSTEM. Anatomy, Physiology, and Surgical Treatment. By JAMES C. WHITE, M.D., Assistant Professor and Tutor in Surgery, Harvard Medical School; Assistant Visiting Surgeon, Massachusetts General Hospital. Pp. 386; 96 illustrations. New York: The Macmillan Company, 1935. Price, $7.00.

IN the past decade surgery of the autonomic nervous system has found increasingly fruitful application. This monograph is an excellent summary of its results in various diseases, based on Dr. White's personal experience and on a critical evaluation of the work of others. In a field so rapidly growing it becomes necessary to point out not only "those conditions which are suitable for sympathectomy but equally those which are not." This Dr. White does with admirable candor.

In general the objective of sympathetic surgery has been the interruption of either the motor supply of a viscus or the afferent fibers which course in the peripheral sympathetic nerves. An example of the first approach is sympathectomy for spastic peripheral vascular disease, of the second, section of the cardiac sensory pathways in angina pectoris. The utility of preliminary novocaine block as a test of results obtainable by permanent nerve section is stressed.

In addition to practical therapeutic results obtainable, knowledge of underlying pathologic physiology of various diseases which sympathetic surgery has revealed should be of the widest medical interest.

The book is divided into sections on anatomy, physiology and experimental technique, clinical results and surgical technique. There is an adequate bibliography and a good index. G. G.

RADIUM TREATMENT OF SKIN DISEASES, NEW GROWTHS, DISEASES OF THE EYES AND TONSILS. By FRANCIS H. WILLIAMS, M.D. (HARV.), S. B., Massachusetts Institute of Technology; Senior Physician, Boston City Hospital; Fellow American Academy of Arts and Sciences, etc. Pp. 118; 12 illustrations. Boston: The Stratford Company, 1935. Price, $2.00.

THIS small volume on radium therapy is written by one of the pioneers in Roentgenology and Radium Therapy in this country and represents the result of 30 years' experience in the use of radium. It is divided into four parts: Part I deals with the nature and properties of radium, methods of measurement and methods of administration, together with a short account of its use in diseases of the skin and superficial new growths. Part II deals with its use in diseases of the eyes and eyelids and Part III with its use in diseases of the tonsils and other lymphoid tissues in the throat.

Dr. Williams states in his preface that his method is based upon the measurements of the absorption of radiation by different substances used as filters, and by different thicknesses of water used as a standard for the absorption by the soft tissues of the body, thus making possible the selection of the amount and quality of the radiations best suited to a given condition. He describes his early experiments with beta and gamma rays, with tests of their therapeutic value. In the section dealing with the diseases of the eyes and eyelids and the tonsils he describes the instruments used and his

technique in the application of radium. He emphasizes the greater comparative value of irradiation of the tonsils with radium as compared with tonsillectomy.

The book is well printed, is well written and holds the interest of the reader. It contains 12 illustrations of instruments, methods of treatment, and graphs of curves showing absorption of the electrons, etc. Such a concise summary, coming from the pen of a pioneer of such experience with the use of radium and who has had ample opportunity to study his results, should be of invaluable aid to every radiologist. R. B.

THE PARATHYROIDS IN HEALTH AND IN DISEASE. By DAVID H. SHELLING, B.Sc., M.D., The Johns Hopkins University and Hospital, Baltimore. Pp. 335; 26 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $5.00.

THIS is an unusually good treatise on the parathyroids, dealing in a thoroughly scientific, critical manner with all phases of the parathyroids, anatomical, physiological, chemical, pathological and clinical. The illustrations are effective, the bibliography satisfactory, and the manner of presentation very pleasing. At a time when so many recent writings on the endocrines are appalingly unsound, it is a great pleasure to find a book such as this that can be whole-heartedly recommended. Particularly practical in his discussion of the differentiation between primary and secondary parathyroid hyperplasia with hyperfunction, which should be very useful to internists and to surgeons in determining rational treatment.

I. Z.

THE CAROTID SINUS AND THE CEREBRAL CIRCULATION. An Anatomical, Experimental, and Clinical Investigation. By ERIK LUND ASK-UPMARK, SWEDEN. From the Departments of Neuropathology, Neurosurgery and Anatomy, Harvard Medical School, Boston. Acta Psychiatrica et Neurologica. Supp. VI. Pp. 374; 74 illustrations and 22 tables. Copenhagen: Levin & Munksgaard, 1935. (Price not given).

ONE section of this monograph (pp. 46–181 contains a detailed description of the author's studies of the anatomy of the cerebral circulation and carotid sinus in 61 animals, representing 27 species of mammals, birds, amphibia, and reptiles; it is illustrated with drawing and includes a consideration of communications between external and internal carotid systems. This careful morphologic study furnishes the basis for selecting the animal or animals suitable for certain experiments and discloses fallacies inherent in many experiments that have been made in the past. The remainder of the book comprises a lengthy presentation of some inconclusive experiments dealing with the influence of carotid sinus reflexes upon cerebral blood-vessels; of case records of patients with brain injuries, tumors, or cranial neuralgias; and of some of the voluminous literature dealing with the anatomy and physiology of the cerebral circulation and the carotid sinus, the mode of regulation of the activity of vegetative centers, and the physiologic disturbances associated with lesions involving various parts of the central nervous system and various cranial nerves. These are some of the most vexing problems in physiology and neurosurgery; a monograph on any of them would be most welcome if written by a person of mature experience and judgment, but a monograph dealing with all of them, written by a young clinician as a result of 2 years' incumbency of a Rockefeller Fellowship, seems to the Reviewer to be a monument to the industry of the author rather than a contribution to scientific literature. C. S.

NEW PATHWAYS FOR CHILDREN WITH CEREBRAL PALSY. By GLADYS GAGE ROGERS, Director of Robin Hood's Barn, A Camp School for Children with Cerebral Palsy, and LEAH C. THOMAS, Director of Therapeutics at Robin Hood's Barn. With photographs by NEWELL GREEN. Pp. 167; 12 illustrations. New York: The Macmillan Company, 1935. Price, $2.50.

BASED upon 17 years experience in working with cerebral palsy cases, in the home, hospital and school, the authors of this useful little volume have evolved a hopeful system of treatment in a group of mentally normal but physically crippled children, a group that in point of numbers is second only to that of infantile paralysis. Throughout the book emphasis is placed upon instilling into these children self confidence in order to banish muscular tension. The parent of a spastic child will gain from this book a clearer insight into the child's emotional life, the physical therapist and the teacher will obtain many valuable leads in regard to methods of treatment and educational materials available and the physician will learn the many minute details ordinarily passed over as trivial. In the story so imaginatively unfolded all will observe the happy rewards of infinite patience. As Dr. Robert B. Osgood, in his introduction, so aptly says: "The book is packed with practicality. Through its pages flows an optimism justified by accomplishment." S. R.

COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, VOLUME III. Pp. 359; illustrated. Cold Spring Harbor, L. I., N. Y.: Long Island Biological Association as a part of the work of The Biological Laboratory, 1935. Price, $3.75.

THIS third volume of The Cold Spring Harbor Symposia is concerned with "the interaction of ourselves and things around us with light." It will be recalled that the two previous symposia dealt largely with surface phenomena and some aspects of growth (see Reviews in this journal, **187**, 851, 1934 and **189**, 577, 1935). The 36 communications deal with photochemistry, chlorophyll, photosyntheses, photosyntropism, bioluminescence, radiation, vision, photosensitization and so on in a highly technical and quantitative manner that would make an adequate review difficult even for the superscientist who possessed adequate knowledge. As a storehouse of the most recent information and a statement of modern theory by competent authorities the book is valuable and has its interest for many.

E. K.

A TEXTBOOK OF BACTERIOLOGY. By THURMAN B. RICE, A.M., M.D., Professor of Bacteriology and Public Health at the Indiana University School of Medicine. Pp. 551; 121 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, $5.00.

DESIGNED both for the practising physician and the medical student, this text contains excellent and ingenious advice concerning many technical procedures adapted to limited time, material, and equipment. A shortened textbook, emphasizing the salient points of diagnosis, prognosis, etiology, specimen collection, interpretation of laboratory findings, specific therapy prophylaxis, etc., this simplified account serves only as a bare introduction to the science of bacteriology. Certain biochemical and physical phenomena are explained too diagrammatically. The importance of the changing equilibrium between host and parasite is not stressed. There are no specific references to the source material. A compact table presents the choice of culture media for simple diagnostic bacteriologic work for eleven classes of

pathogenic organisms (including fungi). There is also a compendium of the various routes of inoculation and the customary uses of each. Five appendices contribute to the value of the book. One deal with special bacteriology which includes the urine, the gross appearance of infected wounds, decubitus ulcers, chronic focal infections and pyrogenic substances in distilled water. Common errors in the technique of collecting samples are pointed to, as the author describes exactly what should be done in each case. There are sections on federal and postal regulations for the sale and transportation of viruses, serums, toxins, etc., and on the technique of practical disinfection. E. B.

BODY WATER. The Exchange of Fluids in Man. By JOHN P. PETERS, M.D., Professor of Internal Medicine, Yale University School of Medicine. Pp. 405; 5 illustrations and 15 tables. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

THIS scholarly book discusses a subject of great importance to an understanding of many physiological and pathological processes. Water is the most abundant constituent of living things; it has unique and remarkable properties of which not the least is its capacity to dissolve so many different chemicals. Life depends upon constant interchange between the cells of the body and its fluids, the blood, lymph and interstitial fluid. It is this exchange as it occurs particularly in man with which the book deals. There are chapters on the chemical forces that control the exchange of water and of solutes; on the nature and movements of interstitial fluid and of lymph; on the exchanges between blood and interstitial fluid, and between various cells and fluids; on transudates; on the water produced through the oxidation of foodstuffs; on the losses of water through the skin and the respiratory passages; and on the exchanges in the alimentary tract.

These chapters constitute a background for the discussion of the functional pathology of renal disease to which is devoted over one-third of the monograph. In the chapter on the general nature of renal activity the author emphasizes a rôle of the kidney not always properly appreciated in clinical medicine; namely that the kidneys serve not only as excretory organs but that they also conserve selectively, for the further use of the organism, a considerable variety of substances, of which glucose is probably the most familiar example. In states of renal insufficiency the disturbances are due not solely to retention of substances that are normally eliminated, but also to elimination of substances that are normally conserved. In further chapters is discussed the excretion of water, of salts, and of other solutes; and the nervous and hormone control of urine excretion.

For the reader who would pursue in more detail any of the topics there is appended a bibliography of nearly 900 titles. B. L.

DISEASES OF WOMEN. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Gynecologist to the Barnes Hospital, St. Louis Maternity Hospital, and St. Luke's Hospital, etc., and ROBERT JAMES CROSSEN, M.D., Instructor in Clinical Gynecology and Obstetrics, Washington School of Medicine, etc. Pp. 999, 1058 illustrations including one color plate. Eighth Edition, entirely revised and reset. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

THIS edition appears in a new and attractive style of paging and binding. The revision shows a thorough evaluation of the contributions to gynecologic literature of recent years with the inclusion of much new material. The second chapter, which discusses gynecologic pathology, is developed to an

unusual degree. A very logical arrangement of the subject matter brings out in an orderly sequence all morbid conditions of the pelvic structures. Meyer's views on the etiology of certain ovarian tumors are freely quoted. This section is profusely illustrated with photomicrographs of unusual merit. The present edition should sustain the popularity of this standard work. P. W.

THE TREATMENT OF ACUTE POISONING. By H. L. MARRIOTT, M.D., M.R.C.P. (LONDON), Resident Medical Officer, The Middlesex Hospital, London; Assistant Physician, The Miller General Hospital, Greenwich. Pp. 45; 15 illustrations. London: John Murray, for the Middlesex Hospital Press, 1935. Price 5s.

IN a brief and easily readable monograph, the author discusses the treatment of acute poisoning and the therapeutic measures which he has found most satisfactory. He believes that in emergency cases, much valuable time is lost in attempting to recall and administer a specific antidote. It is pointed out that this is seldom necessary since the treatment of all types of poisoning is fundamentally similar and consists of (1) removal or neutralization of the poison and (2) counteraction of its effects. This idea of simplicity is one to be highly recommended, although the book contains little else which is not already familiar to the average physician. L. B.

DER GEBURTSTOD (MUTTER UND KIND). By DR. SIGISMUND PELLER, Pp. 110; 56 tables. Wien: Franz Deuticke, 1936. Price, M. 5.

THE various factors causing Infant and Maternal Mortality are here ably discussed. Not only has the subject been handled by analysis of published statistics but a review of the causes of death is presented from the standpoint of preventive medicine in its broadest sense. Peller feels that the problem of natal mortality is primarily one of physiology and social hygiene, and regards the possibility of reducing the natal mortality of infants to 1% and first week mortality to 0.5% as an attainable end.

Regarding maternal mortality he feels that the specific and non-specific causes of death have not been sufficiently differentiated in various countries to make comparisons equable. The abortion problem, as he points out, further clouds the true picture of obstetrical death rates. Abortion as a single cause of maternal death holds the center of the stage in the world over. P. W.

AUTOBIOGRAPHY, SIGMUND FREUD. Translated by JAMES STRACHEY. Pp. 153; 1 illustration. New York: W. W. Norton & Co., Inc., 1935. Price, $2.00.

THIS monograph is an enlarged and revised edition of the essay published in 1925 in Die Medizin der Gegenwart in Selbatdarstellungen. It is not so much an autobiography as an account of the historical development of Freud's ideas, all of which are presented very sketchily because of lack of space. To those who will be led to read this book in order to obtain a true autobiography of Freud, the work will be a real disappointment. There is no attempt at self-analysis, and no real autobiographical material, except insofar as it affects the development of the theory of psychoanalysis.

One feature of the book is extremely interesting, viz.: Freud's early interest in organic neurology. He was well-trained in physiology, wrote an excellent monograph on cerebral diplegia, one of the first to advocate the use of cocaine as a local anesthetic, and made on of the first diagnoses of

acute polyneuritis. Organic neurologists will probably point to these facts to prove that organic neurology is the backbone of all neuropsychiatry, when in truth it only demonstrates that Freud's was a very keen and alert mind which was capable of superior work in whatever field it was interested.

The account of the birth of analysis, its development from hypnosis, and the schism between Breuer and Freud is told frankly. Freud does not hesitate to discuss freely his quarrels with his other dissenting disciples such as Jung and Adler, but none of his accounts become polemic. Some account is given of the struggle for recognition of psychoanalysis, but none of it bitter.

The book is very readable. The translator has done such an excellent job that one is rarely aware of reading a translation. The book may be recommended for a sketchy account of Freud's theories, and for a few fragments of Freud's intimate life. B. A.

NEW BOOKS.

The Microscopic Anatomy of Vertebrates. By GEORGE G. SCOTT, PH.D., Professor of Biology in the City College, New York City, and JAMES I. KENDALL, PH.D., Instructor in Biology in the City College, New York City. Pp. 306; 167 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $3.75.

Medical Mycology. Fungous Diseases of Men and Other Mammals. By CARROLL WILLIAM DODGE, PH.D., Mycologist, Missouri Botanical Garden; Professor, Henry Shaw School of Botany, Washington University, St. Louis. Pp. 900; 142 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

Clinical Miscellany, Volume II, 1935. The Mary Imogene Bassett Hospital, Cooperstown, N. Y. By NINE CONTRIBUTORS. Pp. 218; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $3.00.

Bibliography on Blood Transfusion, Vol. I. (International Bibliography on the Problems of Blood Transfusion and the Theory of Blood Groups, 1900–1933.) By DR. E. KOENIG. Pp. 226. Leningrad: Professor E. Hesse, 1935. Price, 12 p., 50 k.

Folk-lore from Adams County, Illinois. By HARRY MIDDLETON HYATT, M.A. (OXON.), D.D., Director of the Alma Egan Hyatt Foundation; Officier d'Académie Française; Officier de l'Ordre de la Couronne, Royale de Belgique. Pp. 723. New York: Alma Egan Hyatt Foundation, 1935. Price, $6.00.

Das Hämorrhoidalleiden. Seine Komplikationen und Deren Behandlung. By DR. KASPER BLOND and DR. HERBERT HOFF. Pp. 121; 50 illustrations, many in colors. Wien: Franz Deuticke, 1936. Price, Paper, M. 12; Bound, M. 14.40.

Differentialdiagnose in der Inneren Medizin, Part I. By PROFESSOR DR. MED. O. NAEGELI, Direktor der Medizinischen Universitatsklinik, Zürich. Pp. 216; 55 illustrations, some in colors. Leipzig: Georg Thieme, 1936. Price, M. 9.60.

The Diagnosis and Treatment of Diseases of the Peripheral Arteries. By SAUL S. SAMUELS, A.M., M.D., Chief of the Clinic for Peripheral Arterial Diseases, Fourth Division, Bellevue Hospital, New York; Chief of the Department of Arterial Diseases, Stuyvesant Polyclinic Hospital, New York, etc. Pp. 260; 51 illustrations. New York: Oxford University Press, 1936. Price, $3.50.

Lobar Pneumonia and Serum Therapy. With Special Reference to the Massachusetts Pneumonia Study. By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc., and RODERICK HEFFRON, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 91; 10 figures, 1 plate. New York: The Commonwealth Fund, 1936. Price, $1.00.

You Must Eat Meat. Fancies, Foibles and Facts about Meat. By MAX ERNEST JUTTE, M.D., Formerly Lecturer on Stomach and Intestinal Diseases, New York Polyclinic Medical School, etc. Pp. 164; illustrated. New York: G. P. Putnam's Sons, 1936. Price, $2.00.

Le Sang des Hypertendus. By GEORGES CARRIÈRE, Professor de Clinique Médicale, and CLAUDE HURIEZ, Chef de Clinique Médicale, a la Faculté de Médeciné de l'Université de Lille. Pp. 386; many tables. Paris: G. Doin et Cie, 1936. (No price given.)

Glandular Physiology and Therapy. A Symposium Prepared Under the Auspices of the Council on Pharmacy and Chemistry of the American Medical Association. Pp. 528; illustrated. Chicago: American Medical Association, 1935. Price, $2.50.

American Chamber of Horrors. The Truth about Food and Drugs. By RUTH DE FOREST LAMB. Pp. 418; illustrated. New York: Farrar & Rinehart, 1936. Price, $2.50.

A History of Science, Technology, and Philosophy in the 16th and 17th Centuries. By A. WOLF, Professor and Senator, University of London; Head of the Department of History and Methods of Science, etc. With the Coöperation of DR. F. DANNEMANN, Professor in the University of Bonn, and MR. A. ARMITAGE, of University College, London. Pp. 692; 316 illustrations. New York: The Macmillan Company, 1935. Price, $7.00.

For and Against Doctors. An Anthology compiled by ROBERT HUTCHINSON and G. M. WAUCHOPE. Pp. 168; illustrated. Baltimore: William Wood & Co., 1935. Price, $2.00.

The Hair and Scalp. A Clinical Study (With a Chapter on Hirsuties). By AGNES SAVILL, M.A., M.D. (GLASG.), M.R.C.P.I., Consulting Physician to Fitzroy Square Skin Hospital, etc. Pp. 288; 54 illustrations. Baltimore: William Wood & Co., 1935. Price, $5.00.

The Foot. By NORMAN C. LAKE, M.D., M.S., D.Sc. (LOND.), F.R.C.S. (ENG.), Senior Surgeon and Lecturer on Surgery, Charing Cross Hospital; Surgeon, Bolingbroke Hospital, etc. Pp. 330; 95 illustrations. Baltimore: William Wood & Co., 1935. Price, $4.50.

NEW EDITIONS.

A Manual of the Common Contagious Diseases. By PHILIP MOEN STIMSON, A.B., M.D., Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Visiting Physician, Willard Parker Hospital, etc. Pp. 437; 53 illustrations and 3 plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $4.00.

Delafield and Prudden's Text-book of Pathology. Revised by FRANCIS CARTER WOOD, M.D., Director of the Pathological Department, St. Luke's Hospital, New York; Director of the Institute of Cancer Research, Columbia University, New York. Pp. 1406; 839 illustrations and 22 full-page plates, many in color. Sixteenth edition. Baltimore: William Wood & Co., 1936. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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DISORDERS OF MENSTRUATION.

BEFORE discussing a few of the deviations from normal in the process of menstruation it might be pertinent to state that in spite of the tremendous advances which have been made in the study of this phenomenon, the actual mechanism has not been definitely determined in all its details. After discussing the various theories of menstruation that have been elaborated during the past century, Fluhmann[1] presents what he believes is the accepted theory at the present time. The sex hormone (prolan) of the anterior hypophysis stimulates the development of an ovarian follicle. As this matures it produces estrin which in turn causes the endometrium to grow. After full development of the Graafian follicle, ovulation takes place and a corpus luteum is formed in the remains of the follicle. The corpus luteum produces a secretion called "progestin" which controls the development of the characteristic premenstrual changes in the endometrium, and in addition estrin is formed in greater amounts than before. This estrin production causes a progressive inhibition of the anterior lobe of the pituitary gland so that the amount of prolan available gradually diminishes. Finally estrin reaches its peak and correspondingly the amount of prolan has diminished to the point that it is insufficient to maintain the corpus luteum. This structure undergoes degeneration which results in the cessation of estrin production and thus a breakdown of the endometrium occurs which is known as menstruation. The absence of estrin now releases the inhibition of the anterior lobe of the pituitary which again secretes its sex hormone to stimulate the development of a follicle in the ovary for the next menstrual cycle.

Shaw[2] has studied the material removed at operation in 36 cases in which the cyclical changes in the ovaries could be examined and in 70 cases in which the cyclical changes in the endometrium could be

observed in order to determine the relation between ovulation and menstruation in women who menstruate regularly with a normal rhythm. He had previously shown that irregular bleeding is characterized by departures from the normal relationship of these two processes. In the present study the time relations of ovulation and menstruation have been investigated with the use of the method of identifying recently ruptured follicles in the ovaries in women who give reliable histories. It has been shown that ovulation is restricted to about the 14th day of the cycle. There is some variation in the time of ovulation but the variation is probably not more than 2 days. A study of the condition of the corpora lutea at other stages of the cycle confirms this view. Indirect proof as to the time of ovulation can also be obtained by examinations of specimens of the endometrium. It has been shown that the secretory phase of the endometrium develops after the 14th day of the cycle. The specific features of the secretory phase are never seen before this time.

For many years, particularly before the present theories of menstruation were offered, it was thought by many gynecologists that frequently irregular and profuse menstruation was due to some pathologic change in the muscular wall of the uterus, hence the terms "chronic metritis," "myopathic bleeding" and "fibrosis uteri" were convenient labels for a condition which was not well understood. Refuting such concepts is the work of Baker,[3] who studied the collagenous tissue of the myometrium of 40 uteri obtained at necropsy and 19 removed at operation. The material consisted of 13 uteri from nulliparas dead from accidental causes, 7 from nulliparas dead from acute infectious causes, 14 from cases in which death was caused by a chronic disease, 10 from cases of acute pelvic inflammation and 15 from cases in which there was a history of abnormal bleeding. Blocks were taken from various parts of the uterine wall and he observed that with the advance in the age of the patient there occurs within the uterine wall a gradual increase of collagenous fibers which ultimately replace the greater part of the muscle. Neither localized nor systemic acute processes have any marked effect on the uterine wall. Chronic diseases have no effect on the uterine wall of young nulliparas but hasten the age of fibrosis in older nulliparas. The uterine arteries show less pronounced age changes than does the musculature. A study of the uteri from cases of idiopathic bleeding in young women showed no increase of fibrous tissue or abnormal arterial changes that would distinguish them from the normal controls. In the elderly women there was often moderate to extreme fibrosis and a varying degree of arterial change, but these alterations were not more prominent than in the non-bleeders of corresponding age. In brief, therefore, he found no satisfactory evidence that fibrosis of the uterine wall is responsible for uterine hemorrhage.

Irregular Shedding and Ripening of the Endometrium. For a number of years Traut and Kuder[4] have found it increasingly difficult to account for the clinical history, as well as the histologic findings of some cases of functional uterine bleeding on the basis of the usual endometrial hyperplasia syndrome. They have come to the conclusion that there are other clinical entities which cause or are associated with metrorrhagia and although they may be hormonal in origin, they are quite

distinct from hyperplasia. They present two entities, one of which has not hitherto been described while the other has been recognized only in the German literature. The usual type of functional bleeding is regarded as being due to endometrial hyperplasia which results from a hypersecretion of estrin or lack of its neutralization by a decrease or absence of luteal hormone. In the condition which they describe as irregular shedding of the endometrium there is an aberration of the secretory or corpus luteum phase of menstruation. In 1 year they found that about 10% of their patients who had functional bleeding belonged in this group. These patients ranged in age from 23 to 50 years and all gave a history of normal periods until they came under observation because of a prolonged and profuse period or of recurrent bleeding immediately following what was supposed to have been a normal menstrual period. Estrin determinations of the blood showed almost complete lack of this hormone. The genital organs were normal and no constitutional disease was noted in any case. Curettage shows a definite and characteristic histologic picture. The stroma is shrunken and composed of many deeply basophilic spindle-shaped nuclei. The spiral arterioles are usually dilated and engorged and occasionally thrombosed. The epithelium is obviously in the corpus luteum or secretory phase which distinguishes the specimen from hyperplasia, which is just as markedly non-secretory in type. In normal menstruation the shedding of the spongiosa is a progressive phenomenon in the sense that there is focal shedding at a given time and that subsequently other foci bleed and shed in succession, so that the duration of the menstrual period is dependent upon the rapidity with which the various local processes succeed one another. It would seem probable that in this type of menorrhagia we have a very much prolonged menstrual period. As the corpus luteum is in the ascendancy during this phase of the cycle, it would seem that it had some causative effect on such a disturbance of function, although the explanation must remain theoretical for the time being. The treatment consists merely in the usual curettage, after which bleeding ceases.

The second entity which they describe differs from both the hyperplasia and the irregular shedding groups, for these represent two different phases of ovarian activity: the first, the Graafian follicle phase, and the latter, that of the corpus luteum, whereas the one now to be considered (irregular ripening of the endometrium) represents both a mixture of both proliferative and secretory phases. In their study of 100 patients with functional uterine bleeding, they found this mixed picture in 21, hyperplasia in 68 and irregular shedding in 11. Histologic examination in these 21 cases showed an endometrium which in the peripheral zone showed areas which were non-secretory and others which were just as definitely secretory. The impression which they gained from a study of the sections was that of a patchy or irregular corpus luteum effect in an endometrium otherwise in the proliferative phase, hence they call this condition "irregular ripening." These patients, like those which have irregular shedding of the endometrium, have responded promptly to curettage and have not had a recurrence of the disease. They are at a loss to explain the non-recurrence, because they feel that the disease has its origin in a quantitative imbalance of

the ovarian hormones which should not be remedied in all cases by simple curettage. The above study is of interest to both the gynecologic pathologist and the endocrinologist; but to the practical operating gynecologists the important point is that all three conditions mentioned respond to curettage, although endometrial hyperplasia may occasionally require some irradiation as well.

Menstrual Disturbances Associated With Low Metabolic Rates. A group of patients who had amenorrhea, oligomenorrhea or menorrhagia and low basal metabolic rates were treated by Haines and Mussey[5] at The Mayo Clinic with carefully regulated oral doses of desiccated thyroid glands. To determine the effectiveness of desiccated thyroid alone in the treatment of these conditions, no patients who received any other form of treatment were included in the study. Definite improvement in the menstrual flow was obtained in 72% of the cases in which there was amenorrhea; in 55% in which there was oligomenorrhea, and in 73% in which there was menorrhagia. Aside from whether or not there was an improvement in the menstrual disturbances, about 75% of the entire group of patients reported improvement in their general health after elevation of the basal metabolism to within the average normal limits. There is sufficient individual variation in the daily dose of desiccated thyroid to make it necessary to hold the basal metabolic rate at the optimal level for the individual patient. Therefore patients were not treated unless they could be kept under observation long enough to work out the necessary dosage. In this group the dosage varied from $\frac{1}{2}$ to 3 grains daily. Because most patients feel best if the basal metabolic rate is held at about -3 to -8%, this level was aimed at in the treatment. It seemed as effective as higher levels in the treatment of menstrual disturbances and was much less likely to result in uncomfortable symptoms, such as palpitation, diminished heat tolerance and weakness. As a rule, thyroid treatment has to be continued for an indefinite period. They have noted that when patients improve on thyroid medication, the discontinuance of the treatment is commonly followed by lowering of the metabolic rate and a relapse to their former condition.

Treatment of Menstrual Irregularities. It is often of great importance to obtain a specimen of endometrium before instituting treatment of functional uterine bleeding in order to differentiate the physiologic responses of the mucosa to one or another type of hormone stimulation. Novak[6] states that the endometrium is the registering board of ovarian endocrine activity and its microscopic study often yields much more useful information than blood or urine hormone studies. For this purpose he has devised a suction curette apparatus which can be used without anesthesia and without discomfort to the patient. The instrument is about the size of the cannula which is used in the Rubin test and is connected with a power suction machine. The test can be done as an office procedure, but strict asepsis should be maintained.

Antuitrin S, an extract of the urine of pregnant women, was administered by Smith and Rock[7] to 56 patients with dysfunctional uterine bleeding. Of these, 28 were cured, 22 benefited and 6 were unrelieved. The cessation of bleeding accompanied treatment so often and in many cases so rapidly as to leave little doubt as to the specificity of the

hormone. These cases usually show ovaries which fail to contain a corpus luteum which secretes the hormone which is supposed to prevent uterine bleeding. The logical treatment, therefore, would be the administration of corpus luteum. Since satisfactory preparations of corpus luteum are not available for clinical use, several investigators have used the extract of urine from pregnant women which contains a luteinizing principle causing the formation of corpora lutea in the ovary. This extract is known by several names, such as antuitrin S, prolan B, follutein, etc. The usual treatment consists of from 2 to 6 intramuscular injections of 5 to 10 cc. over a period of from 4 to 10 days. Each cubic centimeter represents 100 rat units, a rat unit being the smallest amount that will cause luteinization in the ovary of the immature rat. The reactions from the injections are often severe and occur in the form of chills, headache, fainting, nausea, vomiting and fever occurring within 12 hours after injection. They occurred in 21% of the injections in this series. The injections seem to be more effective if given while the patients are bleeding than if given as a prophylactic.

Bakacs[8] has been able to control abnormally profuse menses in 82% of the cases by the injection of parathormone and calcium gluconate, whether the case is simple hypermenorrhea or metropathia hemorrhagica. He uses a preparation called Paracals, which contains 50 units of parathyroid hormone and 100 mg. metallic calcium in the form of calcium gluconate, which is given as an intramuscular injection in the gluteal region. It is of value as a prophylactic treatment in about 70% of cases if injected for 4 to 6 days before the expected period. He believes that the value of the parathyroid extract is not due alone to its action upon the calcium, but that it has some value of its own.

The functional menstrual irregularities in young women have been divided into two groups by Drips,[9] according to the predominant symptom, namely amenorrhea and menorrhagia. In a group of 244 cases of the amenorrheic type treated at The Mayo Clinic which were observed for 1 year, it was found that low voltage irradiation of the ovaries and the hypophysis has proved to be the most valuable therapeutic agent in reëstablishing the menses. It has made pregnancy possible in the more severe cases in which organotherapy failed. In the menorrhagic group, comprising 213 cases, it was found that small doses of radium within the uterus constitute the most effective treatment in the more intractable cases in which organotherapy has failed. It should be emphasized that at this clinic irradiation is not administered until medical measures have been tried without success.

Mazer and Spitz[10] are also enthusiastic about the value of low voltage irradiation of the pituitary gland and the ovaries. They report that 23 of 47 women suffering from severe amenorrhea have been menstruating regularly without the stimulus of incidental pregnancy for periods averaging 2.3 years following such treatment. Eight of 15 women suffering from a milder form of amenorrhea (oligomenorrhea) have likewise been restored to normalcy. In the patient of average size, the technical factors are 127 K.V., 5 M.A., 14 inch distance, 5 mm. aluminum filter for 3 to 5 minutes. This is equivalent to $7\frac{1}{2}$ to $12\frac{1}{2}$ S.E.D. or 50 to 80 R. This dosage is varied according to the size of the abdo-

men and the thickness of the abdominal wall. The central ray (in the pituitary exposure) enters just above and posterior to the midpoint of a line drawn between the outer canthus and the external auditory canal. In nearly half of the patients the pituitary gland and the ovaries were treated simultaneously; in the others the exposures were made alternately at 3- or 4-day intervals. The results were approximately the same in both groups. While roentgenologists do not hesitate to treat the pituitary gland, many of them are reluctant to expose the ovaries even to mild irradiation because of reports that in some cases a temporary amenorrhea has become permanent because of such treatment. It is possible that these amenorrheic women would have developed amenorrhea of a permanent type even without such treatment. In order to determine the effect of their treatment on the ovaries they carefully recorded for a period of nearly 3 years after the treatment, the menstrual cycles of 11 regularly menstruating women, and in none of them was the menstrual rhythm affected by irradiation in doses within the limits indicated above. Nevertheless, they caution that the margin between the safe and the harmful dose is probably a very small one.

Keene and Payne[11] state that in many of the milder forms of functional uterine bleeding, the blood loss is insufficient to require treatment. Change of climate, occupation or mode of living will occasionally be followed by a resumption of normal menstruation, or the menstrual irregularity may cease for no explainable reason. They have found that the use of antuitrin S has been of value in about two-thirds of the patients under 30. Beyond this age the treatment becomes less useful as the age increases, it being almost without value after the age of 40. The present teaching concerning the causes of functional bleeding casts discredit upon curettage as a therapeutic measure and explains its frequent failure, but curettage may be of value in certain cases, particularly in young women, where one might hesitate to use radium. Some of these patients will be temporarily benefited or cured. With temporary relief the curettage may be repeated with the hope that sooner or later normal menstruation will become established. After 40 and in younger women, when other methods have proven unsuccessful, radium or Roentgen therapy is indicated. They prefer radium because its dosage can be more accurately regulated and the beneficial effects are in part due to its local action upon the uterine bloodvessels. It should be remembered that profoundly anemic patients react poorly to both radium and the Roentgen ray, and either form of irradiation should be withheld until the blood has been improved by transfusion and other appropriate treatment. Radium may be dangerous in patients who have had a previous pelvic operation, since an intestinal loop adherent to the uterus may be seriously damaged by the rays. The absence of intermenstrual pelvic pain and severe dysmenorrhea is characteristic of functional bleeding. Their experience stresses the point that when pain is an associated symptom, some organic lesion is usually present, even though examination fails to reveal it, and operation is preferable to radium therapy. With surprising frequency the wisdom of this decision will be proven when the abdomen is opened. The highly nervous woman is a poor subject for irradiation because

of the distressing sequelæ which frequently attend the induced menopause. In this type of woman hysterectomy with ovarian conservation yields better results. Radium is rarely indicated in the treatment of patients under 20. When it is found necessary, the initial dose should not exceed 200 mg. hours. Between 20 and 30, their results show that a dosage of 400 mg. hours can be administered safely. This dosage will be more than 80% efficient in the control of bleeding, but a few patients will develop a temporary amenorrhea of a few months' duration. Should the bleeding persist, the dosage can be increased by 100 mg. hours. Their analysis of the group between 30 and 40 brings out the important fact that with increased dosage there is a rapidly increasing incidence of menopausal manifestations. With a dosage of between 800 and 1200 mg. hours, permanent amenorrhea occurred in 56% and severe menopausal symptoms in 47% of the patients. An initial dosage of 300 mg. hours will control the bleeding in 80% and without permanent amenorrhea. Should reradiation be necessary, an application of not more than 400 mg. hours should be administered, and if this fails, they favor hysterectomy with conservation of ovarian function rather than increased radiation. Functional bleeding occurs most frequently between 40 and 50, and because these women are approaching the time when, in the normal course of events, functional activity will cease, the administration of a menopausal dose of radium has come into common usage. They believe, however, that this is a mistake because of the high incidence of severe menopausal symptoms. In women near 40 they are using a 400 mg. hour dosage. Should this and a reradiation dosage of 500 mg. hours fail, a hysterectomy is advised. In women near 50, increased radium dosage can be used because the incidence of severe menopausal symptoms attending it will be more nearly like those of the uninduced menopause. Between 50 and 60, the results of radium therapy are almost ideal, and maximum dosage can be given because severe menopausal reactions rarely develop.

Dysmenorrhea. The satisfactory treatment of severe dysmenorrhea has always been a problem and in years gone by numerous anodyne drugs have been recommended, many of which were found to be without value, while others helped but slightly. With the advent of the surgical era various types of minor operations were advised, and while some were satisfactory in certain cases, there remained the stubborn severe type of dysmenorrhea which seemed refractory to all forms of treatment. In recent years, following the successful employment of presacral sympathectomy for the relief of pelvic pain in cases of inoperable cancer of the uterus, the suggestion was made that this same operation might be of value in dysmenorrhea and numerous reports indicate that it is being tried and with encouraging results.

Counseller and Craig[12] believe that the results obtained from resection of the superior hypogastric plexus would indicate that the primary etiologic factor in dysmenorrhea is dysfunction of the pelvic sympathetic nervous system. When this dysfunction is corrected by resection the benefits are permanent, while the functions of normal menstruation and childbirth are not disturbed. If menstruation has been abnormal in amount and duration, there is a marked tendency for menstruation to become normal.

Adson and Masson[13] agree that the presacral fibers undoubtedly carry afferent sensations of pain, but it is their opinion that the relief of pain in functional dysmenorrhea is obtained not only by cutting the pain fibers but from interruption of efferent fibers in the presacral group, which supply the bloodvessels in the genitalia and the musculature of the uterus. In order to relieve all pain arising in the region of the ovaries, they state that it would be necessary to strip the ovarian arteries by periarterial sympathectomy or by dividing the vessels. Thus, by resecting the presacral nerve in conjunction with periarterial sympathectomy of both ovarian arteries, it should be possible to relieve pain both in the uterus and in the ovaries. This combined operation is not done by many operators so far as the literature would indicate. Most of the reports that we have seen are concerned with presacral resection alone. Adson and Masson divide dysmenorrheas into two groups: the true functional type without organic lesions, and those which are complicated by gynecologic lesions. As a rule, therefore, at The Mayo Clinic, these patients are operated upon by both the gynecologic and the neurologic surgeons. Before any type of sympathectomy has been performed the surgeon explores the pelvis and corrects the pathologic condition, and if not sufficient change is found to explain the pain, resection of the presacral nerve is performed as a single operation, or it is combined with resection of the lumbar trunk or with periarterial sympathectomy of the ovarian arteries. They have not done many presacral resections but they are convinced that the operation is quite useful, judging from the results obtained in the cases which they have operated upon.

Based on an experience of 21 cases, De Courcy[14] strongly recommends the procedure for the relief of obstinate cases which have proved quite resistant to ordinary measures. Good judgment in the selection of cases is a prime requisite. He uses the same technique as others have described and has had no case in which pain has been unrelieved. He has found that menstruation regularly takes place within 48 to 72 hours after operation, no matter at what time in the menstrual cycle it has been performed. Most of his patients have had to be catheterized for 2 or 3 days, but none of them has had further bladder trouble. Several of his patients became pregnant subsequent to operation.

Wetherell[15] believes that this operation belongs in the domain of the gynecologist; one who is able to analyze the individual case and to determine whether everything has been done in a medical way for the relief of the dysmenorrhea. Furthermore, it is necessary that he be able to judge the necessity for the removal of gross pathologic conditions if found present. It is not merely a question of whether the surgeon is able to resect the plexus, but whether the individual case has been fairly studied and that nothing remains to afford relief except surgery. In the light of previous radical treatment, such as radiation, hysterectomy, or the use of opiates, he believes this operation to be a conservative one, but the ever present possibility of a mortality must be kept in mind and the operation advised only in those cases in which there is definite evidence that no other treatment will help. The operator's experience should be such, that in cases of secondary dysmenorrhea requiring other surgery, the operation will be performed with such

rapidity as will allow enough time for the added nerve resection without jeopardizing this patient. He has found no deleterious effect on libido or future pregnancy as a result of the operation.

As a result of his small experience with this operation, Keene[16] believes that it has a place in the treatment of properly selected cases of functional dysmenorrhea, but its adoption is warranted only when less radical measures have failed. In organic dysmenorrhea, presacral resection may be used with advantage to supplement operations on the pelvic organs. He has found that the operation is ordinarily not difficult, but conditions may be encountered rendering its performance not only tedious but also hazardous.

Kindel[17] has performed the operation in a series of 39 cases with 2 deaths. There were 4 cases which could not be followed although the immediate results were good. Of the remainder excellent results were obtained in 14, in 4 the results were classified as very good, good in 6, fair in 4 and there was no benefit in 5. He also cautions that this procedure should be employed only in carefully selected cases. It should not be used as an immediate procedure, particularly in adolescent girls whose first few periods may be irregular and painful. One-fourth of the patients in this series had been previously operated upon without relief of their dysmenorrhea. It can be clearly seen from all of the above reports that this operation is not to be lightly recommended to the "run of the mill" patient with dysmenorrhea, but when one of the cases of severe type appears and all other types of treatment have failed, this operation may be recommended with a reasonably good expectation of relief from further pain.

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DERMATOLOGY AND SYPHILOLOGY

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SOME CURRENT CONCEPTIONS OF CUTANEOUS ALLERGIC MANIFESTATIONS.

Theory of Allergic Manifestations. The new-born science of allergy is going through a variety of very interesting changes and one might say experiences in its efforts to apply and accommodate itself to the behavior of the skin. It is proposed in this summary to editorialize to a certain extent on the publications of the past several years rather than to attempt a complete and meticulous review of a literature so enormous that even constant special attention can scarcely keep track of its innumerable ramifications.

One of the best evidences of flux in a field of knowledge is confusion in terminology and controversy over names. The prime example of this with respect to allergic phenomena in the skin is the discussion which has waged about the term eczema. Eczema has always been a subject of controversy among dermatologists, the morphologic school attempting morphologic differentiation, the histopathologic school attempting histopathologic differentiation, and more recently the newer etiologic and functional viewpoint attempting differentiations based on multiple causative factors and on functional changes as distinguished from structural alteration or clinical lesion. With a perspective of 20 years it is particularly interesting to observe how the old arguments over the significance of oozing, crusting, fissuring, thickening or lichenification, and similar signs as differentiating between dermatitis and eczema, have gradually branched out on the European side of the Atlantic into an effort to define eczema as a specific reaction on the part of a specific group of cells, namely, the epidermis. As the more or less opposing side of the argument, emphasis has been laid by another group on the differentiation of eczema from dermatitis on the score of an individual predisposition in the former, a background, a general susceptibility, or the interplay of various elements including infection,

vasomotor and sweat function, neurogenous factors and functional disturbances in various structures of the body as well as focal or localized infections (other than cutaneous). These are regarded by this group as the setting for the stage or the etiologic scene, so to speak, on which the actual dermatosis develops.

In the main we believe it may be said that within the functional group the allergists have tended at first to emphasize the local factors in opposition to or with a reluctant disposition to compromise with those who have continued to insist upon the great importance of the individual makeup and the predisposing background of the patient. In Europe, some of the most striking and particularly satisfying advances have been made by the Jadassohn and Bloch school of dermatology. The demonstration by them of specific cutaneous allergic susceptibility, their emphasis upon the localization of the shock structure in contact dermatitis to the epidermis and the definiteness with which they have been able to define the exciting or "trigger pulling" causes in many previously ill-defined eczematous manifestations has aroused general admiration and has very properly given their pronouncements extraordinary weight. For other than European, or one might almost say German-speaking students of cutaneous disease, however, the appreciation of and general acceptance of these views has been retarded by a difficulty involving terminology. The limitation or appropriation of the term "eczema" traditionally carrying for English-speaking people at least an aura of the indefinable or *ipso facto* constitutional background, has obscured rather than clarified the situation, at least for the time being. It should be clearly understood by all students of cutaneous allergic phenomena that eczema in the mouth of European, and particularly of German or Swiss trained, dermatologists means a dermatitis resulting from the specific irritation of a specific group of epidermal cells and nothing else whatever. Other forms of inflammatory reaction on the part of the skin are not in the estimation of this group of observers to be rated as having title to the name eczema, however much they may seem to conform in clinical appearance to the conventional morphologic and structural appearances of what for English and American dermatologists has been eczema for considerably more than half a century. On the other hand, dermatitis with purely locally acting causes, which disappeared on removal of the irritant, and which for the English and part of the Viennese school has been dermatitis and not eczema, has been included by the new group in "eczema." For English-speaking dermatologists, and some Europeans until very recently, no such specific allergic sensitivity on the part of a particular group of epidermal cells was recognized. Eczema for them meant a morphologic and evolutionary picture which, beginning as a dermatitis, evidenced a tendency to persist and to undergo a succession of clinical and histologic changes toward chronicity which seems to indicate a profound involvement of the entire skin, to say nothing perhaps of the entire individual.

Emphasis on the individual as a predisposing background at first held a relatively small place even in the thinking of the English-speaking group of dermatologists. This was an inevitable result of the process by which dermatology separated itself from general medicine and made

itself, at the start at least, a morphologic specialty. There was an inevitable tendency to emphasize morphologic characteristics and eczema, therefore, became a morphologic designation, clinical in character and with only a shadowy and ill-defined relation to a general medical or individual predisposing background.

Of late, however, British dermatologists have come to issue in the light of the newer knowledge. One now witnesses the splitting off in the one direction of a group represented say by Adamson[1] in recent discussion (reference may be made to recent editorial[1a]), who accepts in the main the German view that the term eczema should be applied to a specific localized sensitivity phenomenon. On the other hand, one sees an equally determined and effective group represented in the utterances of Ingram,[2] who insists that eczema comes into existence and is definable only in terms of the predisposed or constitutionally susceptible individual. In other words, a specific irritant can provoke a dermatitis under certain conditions in everybody, but certain specific irritants are capable only of provoking dermatitis in individuals presenting a definite predisposing background. The first type of dermatitis is dermatitis venenata, or contact dermatitis. The second type of dermatitis is *eczema*.

While the English-speaking point of view has been somewhat tardily developing and accommodating itself to the advances introduced by the German or Continental group, the Continental point of view has been ably represented in the United States by such observers as Wise, Sulzberger, Peck and their coworkers. These observers have been essentially missionaries for the advances introduced by Jadassohn and Bloch into the understanding of specific allergic phenomena with respect to the skin. No reckoning of significant contributions in the English-speaking field would be complete, moreover, without mention of the intensive studies of Coca and his coworkers, and of Rackemann, Rowe, Duke and other observers in the general allergic field, who have applied their general conception to allergic disease of the skin. Of these observers, Coca especially has made important contributions to the constitutional background problem in his analyses of atopy and of the gastro-intestinal phase of allergic etiology. The general importance of the constitutional side has been studied and discussed in resumé in the past by the Finkelstein group of pediatricians, for example; by Rost, who has attempted to analyze and describe the "late exudative eczematid" and the exudative diathesis; by students of the neurogenic and vascular factors such as Kaposi, Pulay, Sack, Brill and Becker; by French observers from Alibert to Darier; and by general clinical observers such as Stokes and his associates.

The contributions of Coca and of Sulzberger, Peck and their coworkers have concerned themselves within the last several years with an improved definition of the various types of allergic manifestations which may present themselves on the skin and in an effort to define (or one might without impropriety say, to theorize on) the identity of the shock structures involved. Coca[3] classifies three common types of allergic skin disease with reference to specific etiologic diagnosis and treatment as follows, the tabular presentation referred to combining his own views with those of Sulzberger and Wise. The first group

includes the *atopic dermatoses* excited by water-soluble antigens, food proteins and inhaled substances. These are tested with aqueous or dried extracts, by intracutaneous, scratch or indirect (Prausnitz-Küstner or passive transfer) methods, show a relatively short reaction time with wheal and erythema, and are to be treated by avoidance if practicable, and if not, by desensitization if possible. The second group includes *contact dermatitis*, which is usually distinguished by its non-familial character, is due to non-antigenic substances, often simple chemicals and vegetable oils, to be tested for by the original material or its extract, using the surface contact or patch test. The reaction time in this group of dermatoses is usually several hours to several days, or even weeks; the reaction is a local, erythematous, and vesicular dermatitis with no production of antibodies, and the treatment is essentially that of avoidance with occasional successful desensitization, especially where vegetable oils are responsible. The last group includes the *fungus dermatitides*, including the eczematous dermatophytids which are the products of hyphomycetes and molds. The test material is the filtrate of broth cultures, the test technique the intracutaneous or patch, the reaction time several hours to several days, and a positive reaction is manifested by an inflammatory papule with eczematous dermatitis without formation of antibodies. Desensitization is considered by these authors as often successful but rather tedious.

Sulzberger, Wise and Wolf[4] have vividly presented in diagram form the current views of their group with reference to the shock structures involved in cutaneous allergic disease. In eczematous reactions, the first group of common allergic dermatoses, the shock tissue is the epidermis; the reaction time, 24 or more hours; the characteristic lesion, spongiosis and intra-epidermal vesicle formation. The causative substances are frequently simple chemicals or products of fungi. Emphasis should be laid in this statement on the spongiosis and intra-epidermal vesicle formation which is accepted by many Continentally trained observers as almost equivalent to a histopathologic diagnostic criterion for "eczema" in the European sense of the term. The second group of common allergic dermatoses, according to these authors, is the tuberculin-trichophyton type of reactions (not infrequently combined with eczematous responses). In this case the shock tissue is the upper cutis or cutis, the reaction time from 24 to 48 or more hours. The characteristic lesion is the lymphocyte and the later epithelioid cell infiltration. The causative substances are usually microörganisms, bacterial or fungus products; the allergic manifestations of this group being then essentially those of "allergy of infection." The test procedure for the tuberculin-trichophyton type of reaction is intracutaneous injection with a reaction time of 48 hours. The third group of common allergic dermatoses, as defined by Sulzberger, Wise and Wolf, are the urticarial reactions. In these the shock tissue is the upper cutis, particularly the bloodvessels, and increasing emphasis is being placed by these authors on the bloodvessels and their relation to blood-borne allergic excitants. The reaction time to intracutaneous, scratch or indirect tests for vascular allergy is from 10 to 30 minutes, the reaction consisting of immediate wheal and flare formation, the characteristic histologic lesion being edema with extravasation of fluid and eosinophils

(wheal). The causative substances for this group of allergic reactions in the skin are foods, inhalants, and the products of microörganisms. The fourth group of common allergic dermatoses is labeled "miscellaneous" and includes drug eruptions, phytids, pyids and other "ids." The shock tissue in these cases is regarded as the deep cutis, epidermis and hair follicles, the reaction time from minutes to days, the lesions multiform in character, including nodules, fixed polychromatic areas, multiform dermatoses and follicular lesions. The histopathology is not specifically defined, the substances responsible include chiefly drugs and microörganisms and the test procedures which are rated as usually inconclusive, include the patch, Moro, or intradermal techniques.

In this summation, then, one has a fairly well-defined picture of the "localist" viewpoint with respect to allergic dermatoses. It will be noticed that at no point does the description cited raise the question of constitutional predisposition, except in the atopic group, as originally described and elaborated by Coca, particularly from the standpoint of the heredity, and the tissue irritability element. Thus far, we believe, it is to be generally conceded that the localists, if one may call them such, have been unable to define what it is that constitutes the irritability, allergic responsiveness, hypersensitivity, or whatever other term may be adopted, which actuates the individual cell of the shock structure in its extraordinary behavior toward what for normal persons are very ordinary contacts.

It is on this point that the attention of those who aim to expand the conception of eczema in the direction of the study of the predispose or eczematous habitus, diathesis, constitution, etc., wish to concentrate their attention. In Ingram's presentation of the constitutionalist viewpoint and in the next two sections of this summary, principal attention is, therefore, given to the factorial interplay in allergic manifestations and to the recognition and study of the predisposing background. Even the most determined localists are coming to recognize that the entire story is not told when the individual reaction has been limited to a shock structure and histologically or clinically defined therein. There still remains an enormous and as yet relatively unexplored field of general medicine and etiology which under various names, as above mentioned, constitutes the stage setting for the crucial act of allergic response, to use one form of metaphor, or the "load" of the human gun which explodes with the "trigger pull" of an allergic excitant.

Factorial Interplay in Allergic Manifestations. One of the most useful conceptions in dealing with analyses of the allergic state is that of multiple etiology. So long as an observer adheres either in his mental evaluations or his experimental attack to a single-cause view of disease phenomena, at least so far as the skin is concerned, he inevitably, sooner or later, finds himself confronted with a hiatus between the results of his theorizing and the effects of his practice. In other words, he clears up his patients temporarily by the removal of what he defines as a causative allergic agent, and then finds them inexplicably and quite inexcusably relapsing with, in a varying proportion of cases, no satisfactory local explanation. He may identify a single allergic excitant or a number of allergic excitants, only to find, following an investigation of the relapse, that the patient now appears to be sensi-

tive not only to the original exciting substance or substances, but to a number of additional substances. In some cases, these substances belong in the general chemical or group category of the originally identified excitants; in others they belong to entirely different groups. In some cases, the patient has clearly lost his sensitivity to what was rated as the original excitant, and developed sensitivities to other excitants which were clearly recognized as negative, or at least as producing no cutaneous response in the original investigation. These paradoxical situations have done more than anything else, perhaps shortsightedly, to discredit allergic study of cutaneous etiology and have given those with limited experience distrust rather than confidence in the ordinary types of allergic work-up or investigation. It is not until a general examination of the entire situation discloses the development within the patient as a whole of new complicating factors or a lighting up of old and previously quiescent ones, that a possible explanation of some of the changing surface allergies comes into existence. To cover this situation, a phrase was developed comparatively early in the study of allergy with respect to the skin and other structures, which is now one of the most useful of all the combinations of words available in this magnificent field in explaining what we cannot explain, or at least in labeling it. This phrase is "broadening the base." (Urbach has recently spoken of parallergy and metallergy.) It is now quite clearly recognized that numerous influences, many of them constitutional both in their general involvement of the body, and in the methods and investigation necessary for their detection, can alter the allergic behavior of the skin. A general or a local infection is capable of bringing into existence, or at least rendering effective allergic predispositions previously completely unrecognized, and perhaps, *ipso facto*, non-existent. Similarly, the dose, so to speak, of an allergic irritant applied to a shock structure seems capable of driving it into frenzy, so to speak, and bringing about an extended or multiple sensitivity which includes far more than the allergic response to the original substance or small group of substances first identified by tests or exclusion methods. Bloch, for example, pointed out the ability of the toxic principle of primrose to sensitize all persons in sufficient dosage and to extend the allergic susceptibilities of certain individuals. The state and behavior of the gastro-intestinal tract with reference to digestive ferments, infection, hydrogen-ion concentration, etc., is capable of modifying to a degree highly significant for the skin the production within the tract of allergens and the ease or difficulty with which they are absorbed. A part of the literature on this mechanism is reviewed by Stokes and Pillsbury.[5] Focal infections in other structures, localized infections on the skin with mycotic and pyogenic organisms, are apparently capable of inducing both an extension geographically of skin sensitiveness in involved areas and the development of a general extensive sensitiveness, making possible the clinical phenomena of "ids."

Further notable recent advances in this direction concern the excitation of allergic states by non-allergens, foreign proteins, etc. Among these observations should be mentioned Haxthausen's[6] demonstration that sensitivity to an arsphenamin can be brought about in the human

subject by the parenteral introduction of deazotized horse serum, for example. The increased susceptibility of the atopic and allergically predisposed types of individual to the arsphenamins in intracutaneous tests was demonstrated by Moore, Woo, Robinson and Gay.[7] Sulzberger and Mayer[8] showed that the behavior of guinea pigs with respect to the induction of arsphenamin sensitization varies not only with the season but with the part of the world in which the tests are performed. Striking variations were exhibited between New York and Breslau, apparently not dependent on such influences as diet. Mayer and Cajkovac,[9] from the Breslau Clinic of Jadassohn, showed that the general non-specific sensitivity of the skin in eczematous individuals as well as in those with lichen Vidal and prurigo Hebræ exhibited seasonal variation with peaks in the spring and fall. It is evident, then, that a group of predisposing factors in skin allergic phenomena and sensitivity exists which is not summed up in a description of the site of shock structure or the clinical appearances of the lesions produced by allergic excitants.

In still another field which may be rated as part of the multiple factorial interplay in allergic manifestations, recent advances have been made. This is the demonstration of multiple antigenic factors in seemingly simple and highly specific antigens. Using experimental methods, such as those of Schultz and of Dakin and Dale,[10] Jadassohn and Schaaf[11] have been able to differentiate in bacterial and fungus antigens, including trichophyton and tuberculin, individual antigenic interrelations of a highly complex character. Dakin and Dale, in 1919, pointed out that the crystallin albumen from the egg of the domestic fowl and of the duck behave as distinct antigens for the anaphylactic reactions, the difference between the two being constituted in their physicochemical structure. When the proteins are racemized, the amino acids escaping racemization are not identical in the 2 cases, so that the two albumens, while perhaps clinically indistinguishable, are in reality allergens of a different order. Jadassohn, Schaaf and Laetsch[12] in recent contributions believe that hen egg albumen and duck egg albumen each contains at least two antigens, one of which is identical in the two varieties and the other different. It is apparent, therefore, that etiologic analysis of allergic manifestations is still merely in its crude beginnings and must shortly be carried as far into the field of analytic and synthetic chemistry as the structure and behavior of endocrin hormones.

Another group of factorial interacting influences is the infection-allergic and the infection-contact-irritant interplay. This has thus far been best observed in clinical studies of fungus excited allergies, to which there have been a number of recent contributions. Beerman,[13] for example, in his recent work on leather dermatitis, emphasized the great importance as a sensitizing agent, of the chemicals used in the tanning of leather with respect to susceptibility to fungus infection. Fungus infections may in turn constitute sensitizing agents, rendering the individual reactive to irritants to which he would otherwise be relatively insusceptible. It is hardly to be believed that the mere development of abrasions is the sole explanation of the developed sensitivity, though of course the laying bare of the epidermal shock struc-

ture can logically be regarded as a means of facilitating locally the development of sensitiveness to a particular agent.

Especially may the group of papers concerning themselves with the clinical aspects of arsphenamin dermatitis and its relation to the allergic state, and those describing pityriasis rosea-like exanthems under bismuth treatment[14] be considered as illustrations of the interplay between drug sensitiveness and the fungus infections. Stokes and Kulchar,[15] for example, found that patients with fungus infections, known to be sensitive to arsphenamins flared up at the site of their fungus lesions even under minute amounts of arsphenamin; that some patients with fungus infections were apparently predisposed to arsphenamin dermatitis and that one patient even over a period of some years' observation demonstrated an interrelation between a general allergic state, in which feathers proved to be the excitant of an arsphenamin dermatitis on one occasion, bismuth on another and a fungus infection on a third. The pityriasis rosea-like and extensive "dermatophytid" exanthems now known to be associated with bismuth reactivity are apparently, at least to all clinical appearance, drug excited explosions of cutaneous allergic phenomena and infections. Still another group of interrelations between fungi and non-bacterial allergic excitants has been illustrated by the observations of White and Taub,[16] who showed that fungus intertriginous mycoses of the hands may be predisposed to by contact allergic excitants such as cake flour, for example; and that no lasting recovery can be secured until the presumably protein allergen is excluded from the picture.

Yet another important group of observations illustrating interplay phenomena concerns nickel dermatitis. Cormia and Stewart,[17] for example, observed a case in which a flare-up at sites of nickel dermatitis occurred in association with an extensive dermatophytic outbreak. The especially prolonged association of irritation by nickel in nickel-plating plants with pyogenic infections, though in part a phase of the general relation between susceptibility to dermatitis and pyogenic infections, is well recognized by students of occupational dermatitis.

While perhaps not entirely classifiable with the interplay phenomena, thus far discussed, it is of interest to note here that it is by no means necessary that allergens producing "eczematoid" manifestations shall attack the skin by way of direct contact with the epidermis. Sulzberger and Vaughan's[18] apparent demonstration that inhaled silk particles are capable of giving rise to eczematous silk allergic manifestations in the skin which could not be excited by actual contact has, however, been disputed by Taub and Zakon,[19] who were unable to confirm Sulzberger's observations, possibly through differences in terminologic rating of the cutaneous manifestations. Neurodermatitis, the condition in question with which both observers dealt, is a term frequently of more morphologic than etiologic significance at the present time. Moreover "neurodermitis" when involved in the eczema-asthma-hay fever complex is one of the most involved of cutaneous etiologic problems. It should be noted too that Taub and Zakon did succeed in proving silk responsible entirely for the eczematous or neurodermatitic manifestations in 3 cases out of the 7 they investigated.

Recognition and Study of the Predisposing Background. The foregoing observations on factorial interplay lead inevitably to a discussion of what seems to be the increasing emphasis placed by both clinicians and investigators on the predisposing background of cutaneous allergic manifestations, and particularly of the "eczema" whose definition we discussed at the outset of this résumé. Even the "localists" are beginning to broaden their horizon and deepen their background. Wise and Sulzberger,[20] speaking editorially in their annual review of allergy and immunology in relation to the skin, provide an exceptionally clear example of the evolutionary changes through which the thinking mind is going in the recognition of the broad background of allergic phenomena. Their remarks deserve quotation in their entirety, for they might and in fact have in one form or another been insisted upon repeatedly by "constitutionalists."

"It is recognized that in allergic disease, the so-called 'cause' is not really *the* cause, but simply the 'trigger' (eliciting) factor. So, for example, horse dander is not *the cause* of a patient's asthma. The conditions of constitutional and acquired nature, the conditions which have determined the patient's peculiar susceptibility to sensitization with horse dander—these, plus the dander, are the causes of the asthma. Gerson (in discussion of whose views their editorial appears) attempts to influence the underlying susceptibilities by diet. This is a praiseworthy attempt and an approach not to be neglected. However, in view of our inadequate knowledge of the fundamental mechanisms at the root of the peculiar predisposition to sensitization, such attempts are, in our opinion, at present still doomed to failure in most instances.

"Criticism is doubtless also true in some measure of attempted cures through the finding and elimination of specific allergens. However, the latter method, which is the usual one today, still promises greater chances of success. Nevertheless, the time may not be too far distant when non-specific measures for reducing sensitivity will surpass in efficacy those of specific investigation, elimination and therapy. This is the goal toward which all of us are continually striving.

"The best method for practical application in allergic disease today consists, in our opinion, of a logical combination of all possible non-specific hyposensitization measures, plus all efforts at specific elimination and/or hyposensitization."

Coming from staunch localist spokesmen, this is indeed a concession to the validity of the "constitutionalist" cause, which must draw enthusiastic appreciation from those who have maintained that predisposing background quite as much as, if not more than local exciting cause, defines the entity (if such there be) of "eczema."

In one of the most important practical studies in the American literature, Eller and Schwartz,[21] dealing with occupational dermatitis, have recently emphasized essential elements in the predisposing background of cutaneous sensitiveness. It should be recalled that in so doing, they have followed in the steps of observers such as Bloch, whose breadth of view on allergic phenomena included generous recognition of a predisposing background; and of Mayer, Prosser White, the most distinguished English exponent of occupational cutaneous disease, Gardiner, O'Donovan, and others including Rost and writers

on "diathetic eczema." It must be realized too that as recently as 1932 Downing and Welch,[22] in reviewing the 10-year literature on industrial dermatoses and their treatment, including the standard works of Prosser White and of Oppenheim, as well as Ullmann, Oppenheim and Rille, plus a summary based on a bibliography of 168 titles, practically omitted from discussion the problem of the workers' predisposition to occupational eczema. Eller and Schwartz, on the other hand, accept the broader viewpoint, in part directly and in part by implication, by giving predisposing significance to age, pigmentation, excessive dryness (ichthyosis) and excessive moistness (hyperidrosis, a nervous phenomenon in many cases), focal and local pyogenic infections, trauma, a predisposition to recurrent skin eruptions which they do not attempt to define, and multiply or "polyvalent" sensitivity. This is manifested in the tendency of a worker who has once become sensitive to one substance to become sensitive also to others. They likewise accept fungus infections as standing in the first rank among predisposing causes, together with their phytid sensitization mechanism and its tendency to induce "polyvalent" sensitiveness. They mention heavy metal poisoning as a possible predisposing agent to allergic response still unproven, and finally speak in general terms of the rough, ignorant, careless and slovenly person with poor hygiene who does not keep his skin clean and who is careless about clean clothes. It was a widely overlooked part of the unusual vision of Prosser White and the English group of students of occupational dermatitis that they recognized the age, exhaustion, overwork, worry and seborrheic factors among the predisposing influences in the background of occupational dermatitis—an emphasis which subsequent students of the subject could do well to imitate.

As further evidence of a broadening viewpoint in the literature, Urbach,[23] among observers, who has recently devoted much attention to the gastro-intestinal factors in cutaneous allergy, closes a discussion of the diagnosis and treatment of nutritive allergic dermatoses by urging that "regardless of the method chosen to eliminate the manifestation of food allergy, the underlying causes of the predisposition should also be sought; these may include foci of infection, neglected gastritis or enteritis, hepatic disease, endocrin disorder, etc. If left uncared for, such conditions may later give rise again to allergic processes not necessarily manifested in the skin."[20]

Diet and its collateral implications has had attention among predisposing elements in the writings of Gerson,[24] well known for his contributions to the salt-free dietary treatment of cutaneous tuberculosis; Anderson and Ayres;[25] and from Zitzke and Peters[26] from the standpoint of acid-base equilibrium. The therapeutic side of Gerson's views is given in the discussion of the dietary treatment of cutaneous allergy, but some of his general observations are in point here. Gerson accepted as a factor in his own case an inherited predisposition to furunculosis. He pointed out the relation between infection and allergic predisposition, insisting that infections become chronic through a summation of allergic predispositions and allergizing infections. He maintained that an exaggerated disposition toward inflammation and spasm exists as part of the background of the individual before the disease, and explains

the failure of recovery. Anderson and Ayers, using the specific instance of erythematous lupus of the disseminate type, in which on clinical grounds there is much reason to suspect a profound allergic hypersusceptibility, cited the startling improvement which occurred in a patient under the diet advocated by a food faddist after failure of the usual therapeutic measures. Subsequently the authors tried this same diet in 6 patients with either lupus erythematosus or active dermatitis. Several of the patients were helped, 1 to the extent of 75 to 80%; 2 patients, 1 with a severe actinic dermatitis, remained unchanged. Zitzke and Peters examined the influence of acid-base equilibrium in connection with the treatment of eczema, pointing out the current differences of opinion regarding the influence of acid-base equilibrium and their relation to complex factors in the food intake, including especially mineral salts and the vitamin content, which they feel may explain the seasonal differences in sensitivity of the skin to irritants. In examining the recent literature on acid-base equilibrium in relation to urticaria, Stokes, Kulchar and Pillsbury[27] found in the main that while there might be such a disturbance it was not yet identified in such terms as to be applicable to any large group of clinical cases. Observers such as Criep[28] and Joltrain *et al.*[29] were unable to find any acid-base disturbance in the blood, while Vallery-Radot *et al.*[30] observed low alkali reserve and were able to reproduce urticaria by reproducing the alkali deficiency.

Continuing the discussion of predisposing causes, Wedroff and Dolgoff,[31] approaching the problem of reactive capacity of the skin by way of the use of obligate chemical irritants in eczematous and healthy persons, observed an increased reactivity of the skin in eczematous individuals which they did not consider to be a phenomenon of allergy. They raised the question as to whether this reactivity was to be explained as a constitutional phenomenon which precedes the eczema and plays a rôle in its pathogenesis, or whether it is to be regarded as a consequence of the eczema.

The influence of the nervous system in the predisposing background of allergic manifestations in the skin has received attention mainly from clinicians who have repeatedly observed the apparent neurogenic background of what is technically called neurodermatitis disseminatus and "diathetic eczema"—the eczema phase of the eczema-asthma-hay fever complex. Attempts to reinforce by test procedures the insistence of some observers on the clinically disordered state of the presumably sympathetic portion of the nervous system in these patients have thus far not progressed as they might, largely because of the relatively unsatisfactory methods for determining the function of the autonomic and sympathetic mechanisms and their balance interrelationship. The older literature was extensively reviewed and aligned by Brill[32] in 1926. Recently Marquardt[33] has studied the problem in guinea pigs experimentally sensitized to ursol. Pilocarpin was found to increase the hypersensitivity, but only if it was injected in the latent period preceding the actual development of manifestations. Atropin failed to lessen the hypersensitivity possibly because of the low response of guinea pigs to atropin. The sedative group of drugs had no particular effect in weakening the sensitization except in the case of luminal.

Carrying over his experiments to man, Marquardt tested normal subjects with adrenalin, atropin and pilocarpin and then sensitized them to ursol followed by retesting. The reaction to pilocarpin was definitely heightened by sensitization, while that to adrenalin and atropin underwent no significant change. This suggested heightened response of the vegetative nervous system he believed to be the consequence rather than the cause of the dermatosis, but was obliged to concede that whether the parasympathetic or the sympathetic mechanism responded in the sensitization process, was probably a function of the individual vagus-sympathetic balance in the particular individual under test. This, together with the older observations of Szondi[34] and many others that vagus-sympathetic balance differs from organ to organ and structure to structure, in a given individual, as well as in different individuals, seems pretty well to lay on the shelf for the moment the attempt to approach the problem of vagus-sympathetic background in allergic cutaneous lesions by way of the conventional pharmacologic tests.

One of the most interesting contributions within recent years to the neurogenous background of cutaneous allergic response, and one which if confirmed will almost startlingly affect the whole problem of allergy in general, is the work of Diehl and Heinichen.[35] These authors reported, in 1931, that using the urticarial test wheal, following the intradermal introduction of a known allergen, as the test object, they had been able to influence by suggestion under deep hypnosis the actual local allergic response. In 3 subjects, 2 with bronchial asthma and 1 with sensitization to ascaris, it was possible to produce variations ranging between 21 and 81% by suggesting increase or decrease of the size of the wheal under deep hypnosis in comparison with the previously performed control test. While this work has not yet been extended to allergic cutaneous disease, it urgently needs so to be extended and will go far to demonstrate the influence of the nervous system on the actual phenomena of allergy.

No attempt is made here to review the extensive literature dealing with the neurogenous background of the typically allergic phenomenon of urticaria. For this reference should be had to the summary by Stokes, Kulchar and Pillsbury.

Local Factors in Cutaneous Allergic Reaction. Osborne and Putnam[36] summarized from the extensive literature of both America and the Continent as part of a discussion of industrial dermatoses, certain significant clinical facts which can now be regarded as clinically and experimentally substantiated with regard to the local allergic responses of the skin. It has been shown by Bloch[37] that the allergic state can be brought about by substances of a non-protein as well as of a protein nature. The concentration of the allergy-inducing substance is critically important. By a sufficiently large dose in the case of the primrose allergen, Bloch,[37] as above mentioned, was able to produce an allergic state in the skin of 100% of exposed persons. Allergic reactivity is not necessarily a universal affair involving the entire skin. It may be local rather than general, and limited to a circumscribed area which has been subjected to repeated exposure to the allergen. In industrial dermatitis and in the performance of patch tests, this local

allergic reactivity is particularly important and may be confined to very small areas, comparatively speaking. It is in such cases quite useless to perform tests for sensitivity, particularly patch tests, at points remote from the site of eczematous reaction. In all induced allergic states resulting from contact, there is a refractory period of indefinite length during which sensitization does not occur; but when the sensitization does begin there is always a definite interval elapsing between the contact and the induction of sensitization which is spoken of as the latent period. This latter usually ranges from 7 to 10 days. The Continental group headed by Bloch was unable to demonstrate the presence of antibodies in the blood serum of patients with eczematous eruptions by the passive transfer method of Prausnitz and Küstner, but other observers, such as Ramirez and Eller,[38] have claimed successful passive transfers in some cases. In such cases it is possible that the inhalation route and blood-stream distribution of the allergen claimed by Sulzberger and Vaughan[18] for silk sensitivity applies.

The importance of repeated or prolonged contact in sensitizing previously non-sensitive persons to individual allergens has been especially evident in the field of cosmetic dermatitis. Eller and Schwartz[21] call attention to this feature of industrial dermatitis also and state that such patients do not desensitize, and therefore present an especially difficult problem.

The question of the influence of intermittent *versus* continuous local contact, from the standpoint of sensitizing effect, is recently discussed by Wolter[39] in the case of a lensgrinder who showed allergic reaction as the result of prolonged contact with irritants, but the eruptive manifestations appeared only after he had, for varying periods, avoided actual contact with the eczematogenous agent (in this case, a turpentine substitute). From this illustration is drawn the conclusion that continuous contact tends to immunization or desensitization, while intermittent contact prevents an adequate desensitization. The sensitization appears to persist longer than the desensitization, thus permitting successive intermittent contacts to give rise to allergic eruptive responses which do not occur with continuous contact. Eller and Schwartz[21] have observed this phenomenon in industrial dermatitis and speak of it as "hardening" by continuous contact. This "immunity" or insensitiveness (desensitization?) usually lasts only from 1 week to a month after contact is discontinued, and if work with the eczematogenic substance is then resumed the immunizing process must be repeated. Wise and Sulzberger[40] state editorially that they have repeatedly observed the same phenomenon and that it is a well-recognized factor in the industrial dermatosis of lacquer workers in Japan.

An additional and important feature of local sensitizing mechanisms is not alone the allergen but the conditions under which it gains access to the skin. Eller and Schwartz,[21] for instance, point out that friction not amounting to actual traumatization is an important element in sensitization induction and state that the failure of patch tests to demonstrate local sensitivity is sometimes due not to inactivity on the part of the allergen but to the fact that the patch tests, as applied, fail to simulate the conditions under which the antigen in industrial contact is applied.

A very important element in local sensitization processes concerns

the hydrogen-ion concentration factor. Stauffer,[41] in 1931, showed that substances with a high hydrogen-ion concentration produced a greater reaction than those more nearly neutral. Recently Burkhardt[42] studied more systematically than previous observers the behavior of the skin under alkalinizing influences. The influence of alkalies in the induction of industrial sensitization had been recognized practically but had been attributed largely to the defatting effect of alkali application. Burkhardt, by the development of a test method, showed that the phenomenon is not one of depletion or removal of protective fat or oils, but that there exists a definite group of individuals who are alkali-sensitive. They are deficient in ability to neutralize alkalies applied to the skin, and show dermatitic response under alkalinizing conditions more readily than do normal subjects. Among non-eczematous persons only 8% have a deficient alkali neutralizing power, while in eczematous individuals 90% have a deficient alkali neutralizing power. This is, therefore, a deficiency in physiologic defense rather than a true allergic phenomenon. Removal of sebum and thickening of the keratin layer of the skin are each powerless to modify the effect of this deficiency in alkali neutralizing defense. Inflammatory changes and age influence the alkali neutralizing defense and probably explain a part of the increased susceptibility to eczematous or dermatitic reactions clinically observed in those already the victims of dermatitic processes or in workers during their later years. Burkhardt and his associates postulate carbon dioxid as the alkali neutralizing agent. The difference in reactivity of persons deficient in alkali neutralizing power and those who are normal in this respect was experimentally established through a study of comparative sensitiveness to nickel dermatitis. Thus recognized allergic phenomenon was shown to be directly accentuated by a deficiency in alkali neutralizing defense.

A final very interesting contribution to the study of local skin allergy, as interpreted by skin tests, was made by Rackemann and Simon[43] through the application of controls in the form of 9 standard allergic cutaneous tests to 60 supposedly normal non-allergic individuals. It is indeed surprising to note that this observer found only 30 of the 60 patients to give entirely negative results to the 9 selected allergens (ragweed, horse serum, normal saline, wheat extract, orris powder, silk floss, cat hair, feathers and timothy). Rackemann and Simon conclude that in clinical allergy many positive tests are obtained but few of them are valuable. Evidently if these observations are confirmed it must be conceded that the non-specific zone of cutaneous reactivity to allergens must be extended far beyond the simpler criteria of obligative irritation due to hyperconcentration, particularly of organic chemical agents and metallic salts.

Allergy in Non-eczematous and Non-dermatitic Eruptions. Acneiform responses and papular eruptions tending to simulate acne vulgaris but determined by the ingestion of specific foods have recently been described by White.[44] This author, in a series of 32 cases with recurrent papular and papulopustular eruptions, points out that clinically the process is differentiable from ordinary acne by the absence of comedones and seborrhea and the more or less complete failure of the ordinary treatment for acne, particularly with Roentgen ray. White

quotes Rowe as having observed similar cases. He calls attention to the negligible value of the usual skin tests in determining the incriminated food allergens, and states that the six most common offenders were chocolate, milk, wheat, oranges, tomatoes and nuts. The method of identification was that of elimination diet and the use of non-allergic foods. Skin tests were rated as of little value in these cases.

Urticaria, generally regarded as a manifestation of cutaneous allergic susceptibility, has been examined through clinical study of fairly large groups of cases by Eichenlaub,[45] Menagh,[46] Criep,[28] Hopkins and Kesten,[47] Fink and Gay,[48] Sulzberger and Rostenberg,[49] and Stokes, Kulchar and Pillsbury.[27] Several of these authors summarize a part of the European literature. From these studies the somewhat surprising conclusion seems to appear that chronic urticaria at least is not solely a cutaneous allergic disease in a very large proportion of cases. At least its allergic status cannot be determined satisfactorily by the conventional tests. Patch tests are generally accepted as of no value. Intradermal and scratch tests yield varying proportions of positive results. Eichenlaub rated 40% of his cases as due to food; Hopkins and Kesten apparently found foods of minor importance, for of 200 cases only 4 involved general food allergy, 13 involved the taking of individual specific foods and 15 presented complicated combinations of what seemed to be food sensitivity with other exciting factors such as cold. From the general picture of the background of urticaria afforded by the various studies mentioned, it appears that urticaria is "a disease of complex rather than single causation." Familial predisposition, gastro-intestinal malfunction, gall bladder and biliary tract disease, focal and intercurrent infection, were conspicuous elements. Positive reactions to scratch tests were obtained in 64% of 28 cases in the Stokes, Kulchar and Pillsbury series,[27] but the exclusion of substances to which the patient gave a positive scratch-test reaction and elimination diets were conspicuously unsuccessful as therapeutic measures, at least when used alone. Sulzberger and Rostenberg[49] rate all forms of skin tests as of very little value. Their account of the etiologic background emphasizes drugs as urticariogenic agents, including the salicylates, iodids, bromids, barbiturates, morphin derivatives, phenolphthalein, ipecac, antipyretics and analgesics and arsphenamins. In their opinion the majority of urticarias are not of an atopic nature. Fink and Gay[48] followed 170 cases from 2 to 10 years, finding 15% with an allergic personal history, 28% with a positive family allergic history, 27% negative to skin tests, and most of the positive skin tests obtained to be of problematic significance. They classified their material into etiologic groups, giving the allergic classification a rating of 20%, as compared with 30% attributable to foci of infection, 18% to the psychogenous factor, 5% to the endocrine, and a residue of 25% to undetermined etiology. In the discussion of this paper Vander Veer, Rackemann, Sulzberger, Cohen tended to stress drugs. G. T. Brown emphasized disorders of the gastro-intestinal tract associated with hypoacidity and abnormal intestinal flora which might be interpreted as having some allergic bearings, and added quinin and ipecac to the drug factors. He stated that he had observed sensitization to grass pollen and orris root without hay fever, to be responsible for urticaria.

Gay in closing the discussion stated that eggs, milk and wheat were the chief food offenders, and atophan should be included among the offending drugs.

While purpura and erythema multiforme have been recognized for some time as having in some instances an allergic background, Eyermann[50] has recently reported 18 patients in whom purpura followed the deliberate ingestion of food. Skin tests in 10 patients indicated the offending food in 6. A considerable range of associated allergic manifestations and etiologic foods is described, with egg, milk, wheat, chocolate, beef, potato, oatmeal, string beans and pork leading the list in order of frequency.

Skin Tests. The past several years have seen a curious combination of extension, better differentiation in methods, and greater distrust or more conflicting results in certain methods of skin testing. In general, the tendency has been, so far as dermatologic practice is concerned, toward a decline in the use and acceptance of scratch tests for the recognition of cutaneous allergic states, and a growing emphasis on the patch test of Jadassohn and Bloch, popularized in the United States through the work and writings of Sulzberger, Wise, Peck and others. Jadassohn's original observations on the patch test phenomenon apparently date to 1895, and a full account of the procedure as developed in the clinics of Jadassohn and Bloch is given by Sulzberger and Wise[51] for the American literature in 1931. The immense importance of the patch test for industrial dermatology has been emphasized by Osborne and Putnam,[36] and by Eller and Schwartz,[21] in their extensive studies. It is interesting that Downing and Welch's[22] review of the literature of industrial dermatoses for the 10 years preceding 1932 contains no mention whatever of the recognition of the etiologic agent by patch test, the taking of a careful history and familiarity with the technical processes of various industries and the risks to which workers might be exposed, constituting the larger part of the diagnostic armamentarium.

The literature of the past several years has brought out a number of interesting and important points with reference to the selection of test methods and the value of particular types of test in the detection of allergic phenomena by way of skin or involving the skin as the shock structure. The patch test was regarded by its originators as primarily a test for epidermal sensitiveness, and hence of particular significance in eczema, as defined by European investigators. It was not expected to yield significant returns in urticaria, for example, in which the shock structure is vascular rather than epidermal. As between scratch and intradermal tests, Sulzberger points out that the intradermal test is one for the vascular shock structure and is, therefore, relatively inapplicable to the detection of the etiologic factors in contact dermatitis or eczema. Bloch insisted from the start, however, that the scratch method should likewise be regarded as a test for sensitiveness of the vascular tissues and stated that it was of little if any value in testing for the hypersensitivity underlying the eczemas of adults. Rowe, however, points out that the well-performed scratch test has great value in detecting specific sensitivity to food—a conclusion suggested by Bloch's view that the scratch test is of use in identifying the vascular tissue as the shock structure, influenced by blood-borne (and thus often

food) allergens. That there must be, however, a large factor of individual technical performance and interpretation in skin tests must be evident to anyone who reads the widely varying statements regarding the worth of scratch tests in determining allergic susceptibility in and by way of the skin. Rowe, Schloss, Duke, Rackemann, C. J. White, Urbach, and Peck, in studies of a wide range of allergic phenomena, have called attention to the failure to secure positive scratch reactions in the presence of known hypersensitivities, and to the occurrence of positive reactions which are without etiologic significance. Part of the confusion is due as suggested by Rinkel,[52] to the complexity of the allergic reaction itself, which includes atopic, contact or acquired sensitization, drug and serum sickness, and hypersensitivity induced by infection, more or less indiscriminately under the same terminology in common medical use. Rinkel points out that two types of antibodies are involved, namely, blood reagents and specific fixed cellular antibodies within the shock organs; that allergy within localized groups of cells may or may not be permanent; that skin sensitivity may remain while the shock organ loses its sensitiveness; that sensitivity may precede clinical allergic phenomena as well as remain after they have ceased and that sensitization varies in different areas, and in the same area from time to time. Accordingly, he concludes, and in the main the numerous controversies and exceptions in the literature tend to bear him out, that the decision as to whether or not a patient's symptoms are due to allergy cannot be definitely determined by skin tests. They afford only presumptive evidence which he rates at 50% accurate for food, 85% accurate for inhalants. Only 5% of the consecutive allergic cases studied by Rinkel had complete relief of symptoms from treatment based on their skin reactions alone. Rackemann and Simon's[43] control experiment already mentioned, consisting of skin tests performed on 60 supposedly normal non-allergic patients, tends still further to limit the value of skin testing in the interpretation of allergic etiology. Rowe,[53] among those cited, seems to have the greatest confidence in scratch and intradermal tests, but even he is obliged to recognize the existence of false positives and non-specific reactions. Peck and Salomon,[54] in a thoroughgoing study of 50 cases of eczema in infancy and childhood, dismiss scratch tests as without significance in tracing the etiologic factors in infantile eczema, and go over bag and baggage to the patch test as the effective determinant of etiologic elements in this particular type of eczema.

Among important points to be borne in mind in patch testing technique, the following may be collected from the literature. The concentration of the test substance applied by means of the patch is a matter of considerable importance. For average concentrations not likely to give false positives, reference may be had to standard lists, such as those of Sulzberger,[49] Peck,[55] and Eller and Schwartz.[21] Osborne, Putnam and Saunders[56] especially emphasize this factor and point out that chemical burns are not to be confused with positive patch tests. Danbolt and Burckhardt[57] distinguish in their studies of turpentine dermatitis between the toxic and the eczematous reaction, noting that the latter, which is the significant one, appeared after 24 hours and is best interpreted by the use of weak solutions, the strength being

increased if the results are negative. Patch tests should, as previously noted, be performed at or near the site of the dermatitic or eczematous eruption under study. Following the removal of the patch, Peck[55] states that it is desirable to wait 5 to 10 minutes before attempting to read the reaction. A mild reaction according to this author is to be regarded as significant if it recurs repeatedly. The time during which the patch should be kept in contact with the skin has been gradually lengthened by the observations of various investigators, until it may now reach a period of days or even weeks. The majority of patch tests are, however, read in 24 to 48 hours. Delayed reactions may occur in from 4 to 7 days after removal of the patch and are significant (Peck). Positive tests should be repeated within a month (Peck). A patch test previously performed, resulting in a positive reaction which has subsided, may be observed to flare up upon a repetition of the test at some other and even a quite distant site (nickel—Cormia and Stewart,[17] and arsphenamin). Patch tests performed with high concentrations of chemical allergens or irritants in highly sensitive individuals are capable of producing violent and extensive cutaneous reactions. Caution and experience are, therefore, required in their use.

Important New Groups of Irritants Studied and New Lists. It is proper to remark at the outset of any consideration of this topic that the number of the substances capable of inducing allergic manifestations in the human skin is legion, and grows from week to week and month to month as medical literature rolls from the presses. It is impossible to avoid editorializing on the implications of this flood of reports on allergic reactions to every imaginable substance. Nothing would seem to point more clearly to the belief that something more than a growing complexity of industrial processes and a multiplication of obligative irritants is at the bottom of this extraordinary popularity of contact and other forms of allergy. There is a good deal to suggest both in the hereditary background of allergic manifestations of the atopic type and in consideration of the neurogenous, focal infection, and other influences which set the stage for the allergic drama, that human beings are becoming more sensitive as "total persons," and that allergy is to some as yet unknown extent, a disease of ultracivilization. It is impossible to summarize completely the contributions in the field of new allergens. Several authors, however, among them Weber,[58] Downing and Welch,[22] Eller and Schwartz,[21] Senear[59] (woods), Balyeat[60] (cosmetics) have developed valuable lists, to which reference may be had in attempting to identify responsible substances. To Weber's list of 121 reported plant excitants published in 1930 may be added additional reports by Goldstein[61] of chrysanthemum leaf dermatitis, Rinkel and Balyeat[62] of lettuce dermatitis in a salad maker, cases due to the common weed, tansy (Greenhouse and Sulzberger[63]), the important and widely distributed group of weeds of the genus Helenium (Balyeat, Rinkel and Stemen[64]), tulip bulb dermatitis reported by Horner,[65] hyacinth bulb dermatitis reported by Johnson,[66] and Osborne, Putnam and Saunders' group of plant cases, including sensitivity to forsythia, tulip petals, Boston fern, wandering Jew, and a particular species of coleus. Harville's[67] report deals with a contact eczema from a non-antigenic lipoid substance in the leaf of the bleeding heart.

Ragweed dermatitis has recently come into prominence through the report of Brunsting and Anderson[68] dealing with 18 proven cases due to the oleoresin from the plant. Senear's study of woods remains the most authoritative and complete to date with complete lists and a discussion of the literature. Wood extracts as factors in leather dermatitis are discussed by Berman.[13] In the field of cosmetics, Hoffmann and Peters[69] identified methyl heptin carbonate in a facial cream as the active excitant, and Baer[70] identified the same substances as responsible for lipstick dermatitis. Lash-Lure, reported on several occasions as responsible for severe dermatitis, was recently charged by Forbes and Blake[71] with a death which Wise and Sulzberger analyzed, however, as probably due to intercurrent profound infection for which the dye dermatitis merely paved the way. Kulchar[72] reported contact sensitiveness to the anesthetic "avertin" (tribrom-ethanol) in an anesthetist. Examples of allergic reaction to heat and cold continue to multiply, including the reports of Paul[73] and Levine.[74] Wise and Sulzberger state that urticarial reaction to cold is often a familial disease. Bartels[75] and Richter[76] have recently described excellent examples of heat urticaria. In the latter case, complete cure was obtained by subjecting the patient to slight degrees of heat with gradual increase. In addition to the general cataloguing of sensitivity to chemicals, attention should be drawn particularly to nickel dermatitis, for nickel is so universally a factor in everyday life, that sensitivity to it has real significance for the ordinary case, especially in dermatitis involving the spectacle contact areas of the face ("white gold" contains nickel), and eczema of the hands. The characteristics of this, perhaps the only metal sensitization thus far recognized, have been studied in this country by Goldman,[77] Fox,[78] and particularly by Cormia and Stewart.[17] The latter investigators conclude that while in man the phenomenon is generally allergic (Burckhardt also) it cannot be induced as a true allergic state in the guinea pig. Among other chemical irritants, Osborne, Putnam and Saunders[56] emphasize the importance of soaps and the sulphonated oils used in their preparation. Van Vonno *et al.*[79] have pointed out that in 28 cases of bakers' eczema, a part at least of the sensitivity is not to the wheat, but to the ammonium persulphate frequently present in the flour. The importance of the careful and detailed analysis of complex food products, occupational irritants, etc., is emphasized and even ingested anilin dyes have been incriminated by Baer[80] when used as coloring matter in foods.

A number of special allergy-inducing agents have had intensive study recently. Among them should be included silk, rubber, leather and rhus, or ivy poisoning.

Silk. Growing interest is manifested in the relationship of silk sensitivity to atopic eczema (neurodermatitis disseminata). Figley and Parkhurst[81] have recently reported 5 cases of atopic eczema in which the major sensitivity was due to silk, and in which the reagin could be demonstrated. All 5 patients had other manifestations of atopy, involving the respiratory tract, and all but 1 reacted to other inhalants besides silk. The authors believe that in atopic eczema silk exerts its effect as an inhalant rather than as a contactant. The authors indeed believe that inhalants play as great or perhaps a greater

rôle than ingestants, in the complex etiologic background of atopic eczema, and quote the case of Rattner and Pusey,[82] in which a neurodermatitis in a young man was definitely proved to be due to the perfume used by his wife. Sulzberger and Vaughan[18] also subscribe to this point of view, and believe that inhalants and the respiratory route of absorption deserve further study in the pathogenesis of atopic dermatitis, urticaria, and some forms of infantile eczema. They feel that allergen-free rooms are just as essential as elimination diets in the treatment of these problems. They have furthermore experimentally proved the inhalation of allergens, such as silk in particular, can cause a definite exacerbation of atopic eczema, and conclude that the elimination of, or hyposensitization with inhalant substances combined with the elimination of, or hyposensitization with food allergens is necessary before reaching the conclusion that a positive skin test is of no clinical significance in atopic dermatoses. Taub and Zakon[19] have not been able to confirm Sulzberger's observations that nearly all patients with atopic dermatitis give a strong reaction to silk, and show the reagins to this substance. The authors have made several thousand tests with silk proteins in hay fever, asthma and various dermatoses, with such a large percentage of negative results that they conclude that Sulzberger's silk protein may have been at fault or contained histamin. It is noteworthy, however, that in the detailed histories of 7 patients on whom they reported 3 cases were shown to be definitely sensitive to silk, and responded beneficially to its complete elimination from the environment. Furthermore, Taub,[83] in 1930, reported 105 reactions to silk from the practices of 60 allergists. Its etiologic significance was proved in 27 patients, 22 of whom had eczema, 4 urticaria and 1 asthma. From these papers we can conclude that silk is definitely to be reckoned with in the investigation of patients with atopic eczema, even though its instrumentality may be proved in a relatively small proportion of patients. Nevertheless, the recognition of its influence is of distinct aid in the evaluation of a problem which hitherto has yielded such comparatively poor therapeutic results.

Rubber. While the dermatitis produced by contact with the chemical substances used in the manufacture of ordinary rubber goods has been long recognized, it is not generally known that the finished products such as rubber gloves or condoms may give rise to contact eczema. In a detailed case of a physician who developed a vesicular eczema following the use of both rubber gloves and condom, Obermayer[84] reviews the chemistry of the manufacture of rubber, and enumerates the substances which are eczematogenic. In the particular patient under discussion, the instrumentality of crude rubber, the chemical substances employed in the manufacturing of ordinary rubber goods and ordinary rubber goods themselves were eliminated, and it was assumed that the irritating agents were formed during the process of cold cure vulcanization. Schwartz and Tulipan[85] review an outbreak of dermatitis that occurred among 8 workers in the manufacture of sheet rubber goods. The new rubber products contained three accelerators and an antioxidant. Four of the 5 patients investigated by patch testing reacted to accelerator A, which consisted essentially of tetramethylthiuram disulphid. One patient was sensitive to all the accelerators, as well as to the anti-

oxidant. Accelerator A has been previously implicated as a cause of dermatitis by Kindel and Hayhurst.[86] Obermayer enumerates all of the accelerators which have been reported to be the cause of dermatitis. All are of complex chemical nature, such as hexylmethylenetetramin, which commonly produces a dermatitis known as "rubber itch." This accelerator is responsible for so much trouble that its use is being discontinued according to Eller and Schwartz. Sulphur is also used extensively in the manufacture of rubber and consequently this substance and its derivatives must be taken into consideration in any attempts to determine the etiologic agent in the production of a dermatitis due to rubber. The recent report of Rattner[87] on sensitization to a rubber condom leads one to believe that rubber sensitivity is probably more common than recognized, and apart from the rubber industry, leads to an investigation of the possible instrumentality of rubber, especially in the form of gloves among physicians, housewives and other occupations requiring protection of the hands. Dermatitis of the eyelids traced to the rubber covering of eyelash curlers has even been reported. An interesting review of eyelid contact dermatitis was made by Hollander and Baer.[88]

Leather. Beerman[13] has reviewed the factors involved in the production of leather dermatitis with particular reference to that induced by contact with leather hatbands. The relatively low incidence of dermatitis due to leather suggests the prominent rôle played by individual susceptibility and the influence of the predisposed background. It is interesting to note that cases have been reported from shoe leather, leather wrist-watch bands, leather jackets and leather gloves, as well as a predominant number of cases from contact with the hat band. As would be anticipated, the manufacture of leather is highly complex, involving preliminary preparation of the hides, tanning with vegetable tannic acids, quebracho extract, sumac and chestnut as well as synthetic tanstuffs manufactured from phenol and hydrocarbons. Subsequently, the leather is subjected to treatment by various dyes, finishes and binders. The author was able to trace one of his cases to sensitization to the synthetic tanstuff and another to the vat dye. The author has investigated and illustrates by cases the interplay of the multiple factorial background of leather dermatitis, and believes that fungus infections probably predispose to leather dermatitis through polyvalent broadening of the sensitivity. Conversely an allergic (leather) dermatitis may predispose to or reactivate a fungus infection as has been investigated and elaborated by White and Taub.[16]

Ivy (Rhus). Although the instrumentality of plants in the production of a sensitization dermatitis has been discussed above, special attention is directed to ivy because of the ubiquity of the plant and the high percentage of persons who are susceptible to it. Spain, Coca and MacNair[89] have shown that 60% of persons react to poison ivy, this figure only being exceeded by the 80% who are allergic to Ascaris. Gowen[90] has recently reviewed the prevention and treatment of Rhus toxicodendron poisoning and elaborates in detail the various methods of treatment which he has found successful. A unique method of immunization has been proposed by Maisel,[91] who advocates the direct application of gradually increasing doses of an extract of poison ivy by means of the daily bath.

Treatment and Recovery Factors. The treatment and recovery factors involved in the allergic dermatoses furnish problems of extraordinary complexity. From the controversial cross-currents of the literature of the last several years, the possibilities and impracticalities of a number of modes of treatment can easily be recognized. Withdrawal of the offending allergen, the logical mode of attack, is confined in its usefulness to comparatively simple problems in which one or two contact agents can be eliminated either by removing the worker lastingly from his contacts or displacing the offending substance in the industry. In everyday life, however, it is increasingly evident that sensitivity is at least as often if not more often polyvalent than monovalent, and one confronts therefore the necessity for removing the patient from a series of contacts which may hamstring him in the ordinary conduct of life. The disconcerting trick of an individual allergen, particularly one involving an infectious agent, of "broadening the base" or inducing polyvalence against the patient's constitutional background or allergic habitus, still further complicates the situation. In the most discouraging example of cutaneous multiple sensitivity, namely, the so-called neurodermatitis disseminata (synonymous for many with the eczema phase of the eczema-asthma-hay fever complex and with the exudative diathesis and "diathetic" eczema), careful observers, as for example Sulzberger and Rostenberg,[49] have finally yielded to the clinical practicalities in the case and have recognized that little short of life under a continuous process of elimination diet and incarceration in allergen-free rooms is possible for the atopic type of individual if the therapeutic problem is approached solely from the allergen elimination side. The impossibility of the situation was earlier pointed out by Stokes[92] in a discussion of the treatment of diathetic eczema. Sulzberger and Rostenberg voiced the clinical experience of a number of dermatologists and allergists that many strongly positive reactions in the atopic individual are not necessarily of etiologic significance in his eczema or neurodermatitis, and this, with their polysensitivity, reduces the therapeutic problem *ad absurdum*.

Granted then that when the number of allergens is sufficiently small and that they are individually removable from the patient's everyday life, the results may be highly satisfactory, the next question is raised when such antigens must or will be restored to contact with the patient. This concerns the possibilities of desensitization. Here again, conflict of opinion is notable. In the first place the mechanism of sensitization is not as yet clearly understood even in its local manifestations in contact dermatitis. Aside from the factorial interplay previously discussed, the actual phenomenon is involved in problems of "silent" sensitization (Bloch, quoted by Beerman[13]) and by the problems of a refractory, a latent, and a reaction period (Sulzberger and Wise[93]), which may range individually and collectively from hours to years under influences which are by no means defined as yet. Opinion on the possibilities of desensitization is pessimistic. While it is widely assumed that continuous or frequent contact with high concentration tends to sensitize, the observations of Eller and Schwartz[21] on industrial dermatitis lead them to the belief that it is continuous contact with a local allergen which results in a measure of desensitization sufficient

to enable the worker to "harden" to the requirements of the industry. Similarly one finds Wolter,[39] above quoted, presenting a case to illustrate the effect of intermittent rather than continuous contact in producing local sensitization. Frühwald's[94] questionnaire quotes Haxthausen, Kranz, Mayr, Urbach and Vohwinkel and Schmidt as rating desensitization procedures as unsatisfactory. Sulzberger and Wise[95] editorially limit the practical use of specific hyposensitization to dermatoses produced by certain oils and secondary fungus eruptions, but speak hopefully of the future. In view of the general differences of opinion as to mechanism and results in the entire field of desensitization, it is not surprising to see experienced observers such as Osborne, Putnam and Rickloff[96] in disagreement with Sulzberger and Wise[97] as to the therapeutic possibilities and value of desensitization procedures in the field of fungus-excited eczema and dermatitis. Even the latter found that while desensitization could be accomplished with trichophytin in 15 out of 18 highly coöperative patients, its value as a lasting protective procedure was questionable and uncertain. Even in the field of vegetable oil dermatitis, Gowen[90] found that all the available methods of desensitization, against Rhus ranging from chewing of the leaves to daily baths (see also Maisel,[91] above) and intramuscular injection of the almond oil extract conferred an immunity ranging only from 1 to 2 years. Evidently, then, the problem of desensitization as a therapeutic technique does not reach its all-time low in the atopic constitution alone, but is a method of questionable usefulness in all fields of cutaneous sensitivity.

The problem of the influencing of the allergic state with reference to the skin by dietary measures is receiving increasing attention, and with it, as may be expected, some paradoxical and conflicting experiences. Within this field one observes as in other problems in allergy a "specifist" group and a "non-specifist" group of opinions. To the specifists belong the efforts to recognize and treat underlying allergic factors by elimination diet (Rowe, C. J. White, for example). Many students of infantile eczema, especially among pediatricians, lay emphasis on the importance of food exclusions in the control of the eczemas and eczematoid dermatitides of infancy, and it seems probable that during this relatively uncomplicated stage of the development of the human being, the simpler types of food sensitivity and the elimination of specific food allergens reach their greatest effectiveness. On the other hand, in the critical study of egg-white sensitization, seemingly one of the most direct and simple of food allergies involving a cutaneous shock tissue, Woringer[98] on the one side contends for the importance of allergy to egg-white in the eczemas of infancy, while Sallenbach,[99] Peck and Salomon,[54] Nitschke,[100] Hill and Sulzberger[101] point out from various angles the inconsistencies upon which this earlier opinion is based, and the probable relative unimportance of egg-white sensitization as determined by cutaneous tests in the diet-induced eczemas of human beings. This illustration at least furnishes abundant discussion material for the atopic and the non-specific background of what were formerly rated as specific cutaneous allergic phenomena.

Urbach,[23] in his recommendations for the general management of nutritive allergic dermatoses, points out that proteins are the most frequent offenders but that carbohydrates, fats, salts, acids, spices

and etheric oils may function as such. Pronounced distaste for a certain food is an important symptom. An overdose of the food in question may establish the relation. The only diet which Urbach concedes to be practically free of nutritive allergens is one of pure sugar, of which he gives 300 gm. per day in a weak tea for a 2-day period with the patient in bed. The usual successive single or simple food additions are made to this non-allergic diet, at 24-hour intervals, proteins being first employed, followed by carbohydrates, fats and the other above-named food elements in successive groups. Urbach recommends as a means of saving time the use of "propeptans," taken ¾ hour before the meal at which the foods will be ingested. If the ingested propeptan protects the individual against the particular food ingested, improvement occurs within 3 days and successive elimination of the propeptans used serves to identify the particular propeptan which is protecting the patient and which corresponds to the protein that acts as his allergen. Desensitization to the recognized allergen may follow the use of graded but exceedingly small doses of the incriminated substance, these doses being of the order of 1 drop of egg-white to ¼ liter of water at the start. The complexity of these methods is evident in the description and as in the case of the Rowe elimination diet will make their practical applicability under the home conditions of most patients very difficult. This is a general criticism of attempts to deal with polyvalent food sensitivities, so that between the uncertainties and at times non-specificity of cutaneous tests for food allergens and the complexities of elimination dieting, the average patient is apt to be limited to an exclusion of the principal offenders as detected by skin tests, plus those indicated by an inquiry into food dislikes and clear-cut food upsets and gastro-intestinal reactions.

Gerson,[24] whose contributions to the salt-free dietary treatment of cutaneous tuberculosis are well known, takes, in part on the basis of personal experience, an exceptionally broad view of the many mechanisms involved in persons presenting what appear to be nutritive allergic manifestations. He points to the fact that not only must the specific allergen be eliminated, but that attention must be given to defective detoxicating power of the liver, its effective capacity for forming antibodies, pathologic modes of splitting up the protein molecules, heightened permeability of vessel walls and altered reactivity in a changed nervous system. He emphasizes that the totality of the allergic constitution must be taken into account. This article, exceptional in its breadth of viewpoint with respect to the complex mechanism of allergic phenomena should be read in its entirety. Gerson points out that the withdrawal of a single antigenic substance may alter the balance between non-specific and specific factors in a way to bring about recovery even though other elements may be completely overlooked. Patients from whom salt has been long withheld will become more sensitive to Roentgen rays and aspirin and less susceptible to infections. His particular formula for the dietary study and treatment of patients in whom this portal of entry of allergens is suspected includes an extremely low salt intake, no animal protein in the first 5 to 7 weeks, exclusion of muscle meat and meat soups, milk, eggs, fish and legumes, a low intake of carbohydrate and a high intake of fluid. The diet is

purposely made exceptionally rich in potassium, calcium and vitamins, and moderately rich in fats. Spices, condiments, tea, coffee and coffee substitutes, chocolate, cocoa, alcohol and tobacco are forbidden because of their irritative effects on the vegetative nervous system, which prepare the way for allergens to take effect. For a régime of this sort, Gerson claims a slow but definite desensitization which the author rates as non-specific in character. Gerson apparently observed the homologue of the situation described by Wolter in which certain specific responses to antigens do not appear until the general allergic state improves through the elimination of the larger part of the incriminated antigenic substances.

Among other more or less non-specific desensitizing measures, using the alimentary tract, one may note the now more or less familiar employment of hydrochloric acid by mouth, based on the fact that a considerable proportion of allergics exhibit hypochlorhydria (alluded to by Brown[48]); high vitamin intake, especially of A and B, referred to by White[44] and Redaelli,[102] and skeptophylaxis. Comel[103] felt that vitamin D, through its effect on calcium metabolism and fixation favorably influenced eczema in general. In connection with the attempt to use vitamin B carriers in the treatment of eczema, sensitivity to wheat must be borne in mind and also sensitivity to yeast as recently described by Biederman.[104] Skeptophylaxis, alluded to by White[44] and Urbach[23] consists in a species of Bezredka or antianaphylactic effect obtained through the gastro-intestinal tract by administering a minute amount of the suspected food $\frac{3}{4}$ hour before the taking of larger quantities as part of the meal. This has a definite immediate protective effect, and if persisted in, is rated by Urbach as a valuable method of permanent desensitization.

Preventive Measures in Industrial Dermatitis. The increasing responsibility placed on or assumed by industrial concerns for the occurrence of industrial contact dermatitis in their employees makes particularly important the recommendations of Downing and Welch[22] and Eller and Schwartz,[21] based on a review of the literature and experience regarding preventive technique. The former authors emphasize easy and accessible consultation with the plant chemist, the maintenance of the workmen in a state of physical and mental well-being, frequent inspection of the employees with immediate removal of those reacting to an irritant, and attention to the hygienic conditions of the place of employment. Informal discussion of industrial dermatoses within the Reviewers' knowledge too often brings out a disposition to secrecy and non-coöperativeness on the part of manufacturing and industrial interests which can only react to their own disadvantage. Eller and Schwartz in great detail point out that many processes involving injurious chemicals can be totally enclosed, the raw materials being sucked up into reservoirs from which they flow into retorts and tanks, merely by the turning of a valve. The finished products may be barreled without the worker's having come in contact with any of the intermediates of the manufacturing process. The worker may in some cases be protected against irritating substances by wearing suitable protective clothing such as rubber gloves, aprons, masks and goggles, and

by the application of protective ointment such as has been described by James.[105] The actual elimination of unessential, strongly eczematogenous chemicals is being carried out. It is important that new workers be carefully examined before being received into an industry for evidence of predisposition, especially where the dermatitic hazard is high. In the factories where synthetic dyes and complex organic compounds are manufactured, new applicants should be patch-tested to the chemicals with which they will be called upon to work, and those found to be hypersensitive rejected. There should be periodic routine examinations of the workers in search of those who have skin and other ailments (especially skin infections J.H.S., V.C.G.) and these should have prompt attention.

Eller and Schwartz emphasize the importance of proper ventilation of work-rooms. If the irritating gas or dust is sucked away from workers there will be fewer cases of dermatitis. Exhaust hoods should be placed over processes giving rise to irritating dusts or gases. Floors should be washed at the end of each shift to remove dust. Cleanliness should be emphasized. Shower baths and lockers should be provided, and their use should be obligatory; work-clothing should not be worn to the street or for everyday purposes; the furnishing of clean work-clothes may prove an actual economy. This is particularly true where oils are used in industrial processes, and helps greatly to prevent oil furunculoses and acne.

The legislation involved at the present time is not uniform in different states, and model compensation laws should be drafted after proper study. The use of expert testimony is subject to many abuses, and for that reason it is particularly recommended by Eller and Schwartz that compensation boards be composed of or guided by the opinions of an impartial group of state-paid physicians, totally divorced if possible from politics, and chosen for their familiarity with industrial processes and industrial diseases. Physicians obliged to deal with industrial cases should be made familiar with the compensation laws of their own state, together with the more important decisions of the higher courts.

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PHYSIOLOGY

PROCEEDINGS OF

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Chemotropism of Leukocytes in Relation to Their Rate of Locomotion.—H. M. Dixon and M. McCutcheon (Laboratory of Pathology, University of Pennsylvania). By chemotropism of leukocytes is understood a directional response on the part of the cells, which move toward

a source of attraction (if the response be positive), instead of moving at random, as is the case in the absence of an attracting body. Whether a leukocyte reacting chemotropically travels faster than one moving at random, that is, whether chemotropism has not only a directional but also a velocity component, appears not to have been decided. In order to answer this question, experiments were made *in vitro* with human neutrophils. Leukocytes were observed with the microscope and, with the help of a drawing ocular, their paths were recorded on paper. From these records the rate of locomotion was computed, first, for leukocytes moving toward bacteria (or other attracting bodies) in the same microscope field, second, for leukocytes moving in parts of the same preparation so far distant from bacteria that their locomotion was at random. The sources of attraction used were S. aureus, S. albus and collodion particles (of about the size of bacteria). Leukocytes in the vicinity of each of these kinds of particles were strongly attracted by them, but their rate of locomotion was no greater than that of cells moving at random. For example, the mean rate of locomotion of leukocytes moving toward collodion particles was 35 microns per minute; for cells moving at random the rate was the same. It is concluded that the chemotropic response does not involve increase in rate of locomotion.

A Critical Study of the Sullivan Method for the Determination of Cystin.—James C. Andrews and Kathleen C. Andrews (Laboratory of Physiological Chemistry, University of Pennsylvania). The cause of the increase in apparent cystin content of aging cystinuric urines, as determined by the Sullivan method for cystin, has been traced to atmospheric oxidation of certain urinary constituents which markedly inhibit the formation of color in the Sullivan method. These constituents are, as a rule, substances with strong reducing properties. Ascorbic acid (vitamin C) is one of these constituents but is responsible for only a comparatively small proportion of this inhibiting effect on the development of color in the Sullivan method. A further search is, therefore, being made to determine the identity of these other urinary constituents. While they inhibit color formation in the Sullivan method they do not reduce dichlorophenol indophenol as does ascorbic acid. The original hypothesis of Brand and coworkers, who postulated that part of the cystin excreted by the cystinuric is in the form of an easily decomposed complex, must therefore be discarded.

Examination of a large variety of compounds to determine their ability to inhibit the formation of color from constant amounts of cystin has yielded the following results. The most effective inhibitors are such reducing agents as ascorbic acid, adrenalin, hydroquinone, pyrogallol, diamidophenol (photographic developers in general) and tannic acid. Hydrogen sulphid and certain cyclic derivatives of cystin (such as cystin hydantoin), which readily produce soluble sulphids under the conditions of the Sullivan method, are equally effective. It is obvious, therefore, that the lower results for cystin given by the Sullivan method, as compared with other methods, and which have been attributed entirely to its greater specificity, may often be due to

its failure to produce a proportionate amount of color in the presence of these inhibitors.

A further class of substances, while effective only in larger amounts, are capable of producing erroneous results in the determination of cystin. These include the simple aldehyds, the sugars (both mono- and disaccharids) and various sugar derivatives such as glycuronic acid, its lactone and certain of its conjugation products.

The observations of Lugg and of Rossouw and Wilken-Jorden concerning the interference with the Sullivan method of certain amino acids when present in large amounts are confirmed. These effects, however, are negligible compared to those mentioned above.

The inhibition curves of adrenalin and ascorbic acid form the basis of a satisfactory method of determining these substances in the absence of other such inhibitors.

Factors Concerned in the Measurement of Serum Volume.—F. William Sunderman and J. H. Austin (Laboratory of Research Medicine, University of Pennsylvania). The studies demonstrate a marked change in the color values of vital red dissolved in aqueous solutions of salts of different ionic strength and ion species, with further alteration in the presence of serum.

A technique of colorimetry has been developed in which two standards are prepared by adding dye to serum obtained from the subject before injection of dye, one standard weaker than the weakest unknown, and the other standard stronger than the strongest unknown. The standards are compared in a colorimeter against a neutral tint filter, giving an optical density of 1 and a No. 75 Wratten filter in the lens system. A straight line drawn through the reciprocals of these readings furnish a valid basis for interpolation of reciprocals of the unknowns similarly read, and from this may be determined the concentration of dye in these unknowns.

A method of using the benzidin reaction has been developed for the purpose of detecting the presence of hemoglobin in serum containing vital red.

The Reactions of Hypophysectomized Rabbits to Epinephrin.—C. Bachman and G. Toby (Laboratory of Biochemistry, McGill University).

Addendum.

In regard to a reference in Dr. Dameshek's article (Am. J. Med. Sci., **190**, 617, 1935) to Seyfarth's introduction of sternal puncture, Dr. D. N. Banerjee, of Calcutta, writes us: "The value of puncture of the sternum in the diagnosis of kala-azar was announced by me prior to Seyfarth as long ago as April, 1932 (*sic*) in the Calcutta Medical Journal (vol. **16**, No. 10, p. 400) and abstracted by C. M. Wenyon in the Tropical Diseases Bulletin (vol. **20**, No. 2, p. 97, 1923). The abstract runs thus: 'Banerjee (Dhirendra Nath) An Announcement. A Preliminary Note on the Diagnosis of Kala-azar by Examination of Bone-marrow—reprinted from Calcutta Med. Jour. (vol. **16**, No. 10, p. 1, 1922). The author announces what he regards as a simple and safe method of examining for leishmania in cases of suspected kala-azar by obtaining marrow from the sternum. The anterior plate of the gladiolar portion

of the sternum is opened by means of a Southey's trochar and material obtained from within the bone by means of a hypodermic syringe. He has obtained parasites from all the cases of kala-azar he has examined. A full report of the results of his investigations will be published later. C. M. W.'" Dr. Dameshek has made the following comment: "Seyfarth in his original communication (Deutsch. med. Wchnschr., **49**, 180, 1923) states that he was led to use the sternal biopsy while working at a hospital for tropical diseases situated on the Ægean Sea. He was there in 1916 and 1917 and found the method of value in the diagnosis of malaria and kala-azar, since splenic puncture was often a dangerous method. . . . If Banerjee's statement is correct, it deserves some notice in the accessible medical literature."

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